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OBSERVATIONS ON THE ORIGIN AND STATUS OF THE SO-CALLED "TRANSITIONAL" WHITE BLOOD CELL*

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Probably the status of no white cell of the blood is so uncertain as that of the so-called transitional cell. The original hypothesis of Ehrlich[1] that this cell was a transition form between the large mononuclear and the polymorphonuclear has long since been discarded, although Sahli[2] still adheres to the view that it is an intermediate stage between the myelocyte and the polymorphonuclear neutrophil. By many (Ehrlich,[3] Emerson, Webster and Simon, in the latest editions of their text-books) it is believed to be a senile form of the large mononuclear. Pappenheim and Naegeli refute the hypothesis that this cell is a transitional form between the large mononuclear and the true polymorphonuclear neutrophil, the former regarding it as a promyelocyte in his scheme of blood-cell origin, while Naegeli, after first describing it as related to the myeloblast[4] concludes that, together with the other mononuclears, exclusive, of course, of those of known origin such as the large lymphocyte, it forms an independent cell type of myeloid origin.[5] As an independent cell type it has also been assigned to the lymphoid system, as coming (1) from the *"Keimzentrumzellen"* (Weidenreich, Pappenheim in his earlier studies, et al.)[6] and (2) from the spleen-pulp and marrow-cord cells of the lymph nodes

* Submitted for publication Aug. 25, 1915.

* From the Medical Clinic of The Johns Hopkins Hospital.

1. Ehrlich, P.: Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes, p. 126, Berlin, 1891, A. Hirschwald.

2. Sahli, H.: Lehrbuch der Klinischen-Untersuchungs-Methoden, p. 894, Ed. 5, Leipzig and Vienna, 1909, Franz Deuticke.

3. Ehrlich, P., and Lazarus, A.: Anemia, Nothnagel's Practice of Medicine, Am. Ed., 1905, viii, 66.

4. Naegeli, O.: Anaemia, Lazarus, A., and Naegeli, O., p. 95, Ed. 2, New York, 1910, Rebman & Co.

5. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, p. 186, Leipzig, 1912, Veit & Co.

6. Quoted by Naegeli, Note 5.

(Meyer-Heineke, Gruber, Türk).[6] It has also been considered an adventitia cell (Sternberg)[6] and of endothelial origin (Marchard,[6] Mallory,[7] Adami and McCrae[8]); and Warfield[9] is so convinced of such an origin for the cell that he suggests the name endotheliocyte. Bunting,[10] recently asserting that it does not come from the endothelium lining lymph spaces, maintains that he has adduced proof of its origin in the germinal centers of the lymph glands. Cabot[11] speaks indefinitely of all large mononuclears as arising, some from the bone marrow and others from the endothelium, and Türk[12] in his latest expression of opinion agrees with Naegeli that the large mononuclear leukocyte is of myeloid origin. It is with the hope of shedding some light on this obscure subject that the following observations, concerning an unusual transitional cell reaction after the administration of salvarsan, are reported.

CASE REPORT

History.—S. W. (Genl. No. 100573), East Indian, aged 29, was admitted to The Johns Hopkins Hospital, Feb. 5, 1915, complaining of shortness of breath.

His past history was of no importance, except that he denied lues, but admitted a gonorrheal infection eight months previously which was followed by a swelling of the testicles for a short time.

The present illness began about six weeks before admission, with shortness of breath on ordinary exertion; this had persisted without any increase in intensity and was the only symptom of which the patient complained.

Examination.—The physical examination on admission showed a blotchy, mahogany-colored pigmentation over the arms, legs, body and back, greatly resembling a healing secondary luetic rash. The axillary and epitrochlear glands were palpable, but small and soft. The heart was enlarged, the point of maximum impulse being best seen outside the nipple line, and the left border of relative cardiac dulness lying 2 cm. outside this line. There was a soft to-and-fro murmur over the apex, the systolic being softly transmitted to the axilla, and a to-and-fro murmur at the base, the diastolic well transmitted down the left sternal margin. Retromanubrial dulness was 8 cm. wide. The pulse was collapsing in quality. There was no arterial thickening. Liver dulness reached the costal margin in the midclavicular line. The spleen was not palpable and the area of splenic dulness was not enlarged. There was a typical scar of a chancre on the dorsal prepuce, and the lower pole of the left epididymis was enlarged. The eyegrounds were negative. Massage of the prostate produced a few drops of cloudy material in which no gram-negative cocci could be demonstrated. His temperature was 97.8; pulse 80; respirations 24; blood pressure 110/75 (Tycos).

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7. Mallory, F. B.: Pathologic Histology, Ed. 2, p. 23.

8. Adami and McCrae: Textbook of Pathology, Ed. 2, p. 446, Philadelphia: 1914, Lea & Febiger.

9. Warfield, L. M.: The Normal Differential Leukocyte Count, Jour. Am. Med. Assn., 1915, lxiv, 1296.

10. Bunting, C. H.: The Blood-Picture in Hodgkin's Disease, Bull. Johns Hopkins Hosp., 1911, xxii, 369; 1914, xxv, 173.

11. Cabot, R. C.: The General Pathology of the Blood-Forming Organs, Modern Med., Osler and McCrae, iv, 610.

12. Türk, W.: Vorlesungen über klinische Haematologie, Part 2, p. 143, Vienna and Leipzig, 1912, Wilhelm Braumüller.

Blood Examination.—Fresh blood, normal in appearance. Red blood cells, 4,720,000; white blood cells, 9,000; hemoglobin 101 per cent. (Sahli).

Differential: Polymorphonuclear neutrophils, 61.8 per cent.; polymorphonuclear eosinophils, 0.25 per cent.; polymorphonuclear basophils, 0.25 per cent.; lymphocytes, 28.6 per cent.; large mononuclears, 8.4 per cent.; transitionals, 0.8 per cent.

Urine: Light color, turbid; specific gravity 1.012; acid; no sugar; faint trace of albumin; a few hyaline casts and pus cells.

Stool negative.

Impression on Admission: Luetic aortitis with aortic regurgitation; moderate hypertrophy of the heart.

February 5. Mercurial ointment, 1 dr., as inunction, q. n., and potassium iodid, grs. xv, t. i. d., begun.

February 9. Wassermann test positive.

February 10. Mercurial ointment, 1 dr., as inunction, q. n. discontinued. Salvarsan, 0.3 gm., in freshly distilled water administered intravenously; no reaction.

February 15. Salvarsan, 0.45 gm., in freshly distilled water administered intravenously. Six hours after administration the patient's temperature began to rise reaching 104 in a few hours, he had a severe chill and then general malaise for four or five hours. Except for a pronounced tachycardia, there was no focal reaction of the aorta made out, and there were no anginal attacks.

February 16. Condition at the end of twenty-four hours about the same. Potassium iodid discontinued. Blood count: red blood cells, 5,144,000; white blood cells, 7,840; hemoglobin 91 per cent. (Sahli).

February 17.—Daily examination of urine showed a specific gravity of from 1.011 to 1.027, a constant slight trace of albumin, and except on day of admission there was no casts noted.

Roentgen Ray Report: Aorta dilated and heart enlarged.

February 18. Diffuse scarlatiniform rash noted over face and body.

February 19. Muscles of legs tender to lightest palpation. Urine decreased in amount; albumin more abundant and many granular casts present. Blood: total non-protein nitrogen, 44 mg.; urea nitrogen, 27 mg.; Ambard's constant, 0.22.

February 20. Legs still tender; now swollen. There was, however, no other evidence of thrombosis. Temperature falling.

February 22. Temperature normal. Phenolsulphonephthalein excretion: after 1½ hours, 34 per cent.; after 2½ hours, 35 per cent.; total for the four hours, 69 per cent.

February 26. Lower extremities showed very little tenderness and no swelling. Sclerae definitely jaundiced. Liver edge about 3 cm. below costal margin in the right midclavicular line. Spleen not palpated and area of splenic dulness not enlarged. Red blood cells 5,600,000; hemoglobin 85 per cent. (Sahli).

March 2. Temperature rose to 102 on the previous evening, and remained at this point. Patient quite deeply jaundiced and liver edge 6 cm. below the costal margin in the right midclavicular line. Left lower leg slightly swollen; showed increased resistance to palpation over belly of tibialis anticus and extensor hallucis longus muscles, and there was marked limitation of dorsoflexion of the great toe.

From February 19 the urine varied in specific gravity from 1.006 to 1.019, the quantity of albumin and the number of casts decreased and there was no blood. Bile had been present constantly since February 21.

Blood: Total nonprotein nitrogen, 20 mg.; urea nitrogen, 10 mg.

March 3. Jaundice still quite marked. One slight epistaxis on this date.

March 7. Some oozing of blood from gums noted. Spleen still not enlarged. Red blood cells, 3,705,000; hemoglobin, 80 per cent. (Sahli).

March 8. Temperature, after running a remittent course since March 2, reached normal. Precordial pain complained of and pericardial friction made out. Stool colorless, showing much fatty acid and fat; gave negative test for bile.

March 16. Signs of effusion in pericardial and both pleural cavities made out. Pericardial friction not noticed since March 15. Roentgen ray report of chest: Huge triangular heart shadow; probably pericardial effusion.

March 18. Stool gave positive test for bile. No discomfort complained of, but pleural and pericardial effusions present, though not so extensive as previously noted. Urine still showed albumin, a few granular casts and bile.

April 9. Temperature normal and patient feeling very well. Still deeply jaundiced and looking quite weak. There were no signs of pericardial or pleural effusion. The heart was enlarged, relative cardiac dulness extending 3 cm. to the right of mid-sternal line, and to the left as far as the anterior axillary line. The murmurs were practically the same as noted on admission. Retromanubrial dulness 10 cm. wide at level of first intercostal space. Liver edge 1½ cm. below costal margin in right mid-clavicular line. Spleen not palpated and area of splenic dulness not enlarged. There was no edema, tenderness or paralysis of the lower extremities. Urine still showed a trace of albumin and a few granular casts. The blood pressure during the patient's stay in the hospital varied between 110 and 125 systolic. Patient insisted on leaving the hospital, and was discharged against advice.

May 30. Returned to the dispensary to be treated for the jaundice, which still persisted to a slight degree. Had been working and felt quite well.

In addition to the findings above noted the reaction of this patient was manifested by unusual changes in the white blood cell picture as may be seen by reference to the table of total and differential leukocyte counts. Except for an acute polymorphonuclear leukocytosis accompanying the pericarditis, the changes were almost entirely in the percentage of the true so-called transitional cells described below. The differential counts recorded in the table were made on smears stained by the Romanowski method (Wilson's modification) and these were checked in each instance by counts on smears made at the same time and stained with Ehrlich stain.

DESCRIPTION OF CELLS CONCERNED IN THE REACTION

Those cells classified as transitionals (Fig. 1) in the differential counts in this case were always as large as, and generally larger than, the polymorphonuclears, and varied in diameter from 10 to 20 microns. The nucleus in each cell was irregular and in most of them typically indented or saddle-bag shaped, the protoplasm was abundant and the cell boundaries sharp and even. Stained by the Romanowski method (Wilson's modification) the nucleus appeared rather densely reticulated and of a dark purple color. The protoplasm was a pale blue and quite thickly set with an apparent fine neutrophilic granulation much resembling that seen in the polymorphonuclear neutrophil, and occasionally seeming to overlie the nucleus. In a few cells large azure granules suggesting those encountered in the protoplasm of the large mononuclears were also present. Stained with Ehrlich's stain

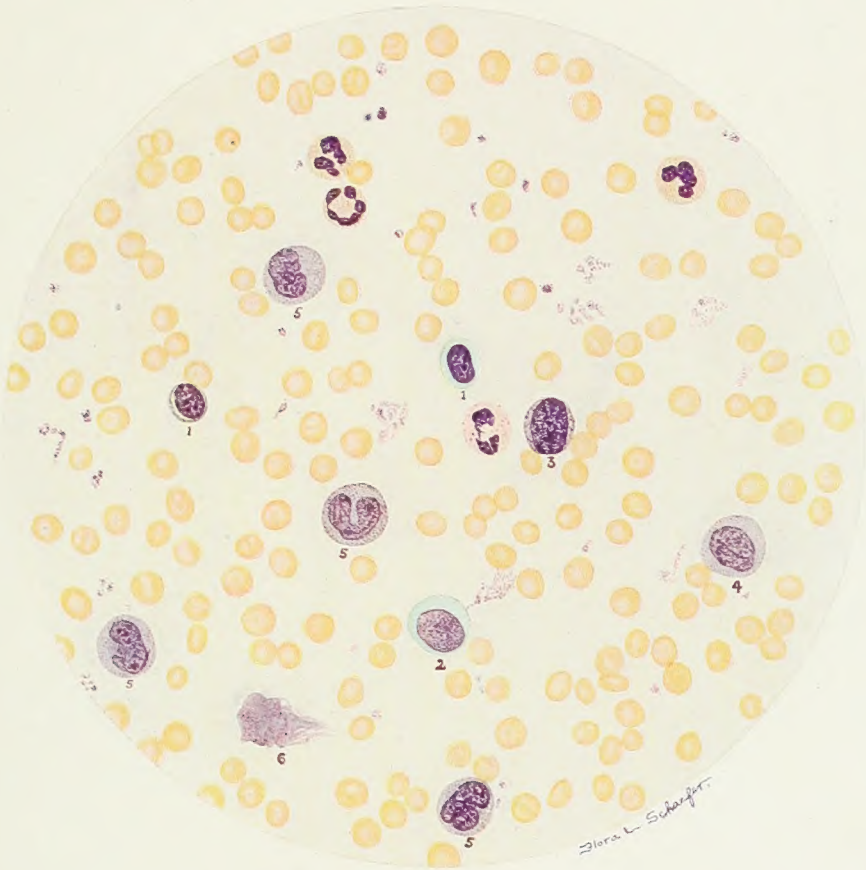

Fig. 1.—Field taken from smear made March 16 and stained with Wilson's stain, showing some types of cells encountered and illustrating their classification. The evidence of mild secondary anemia present in this field represents fairly accurately the true condition at this time. 1. Small lymphocyte. 2. Large lymphocyte. 3. Large mononuclear quite different from the transitional. 4. Large mononuclear closely resembling the transitional. 5. Transitional. 6. Degenerated cell — unclassified. Although 4 definitely and 3 quite probably belong to the transitional cell group, both were included with 2 and classed as large mononuclears.

Illustrating Article by Frank A. Evans, M.D.
The Archives of Internal Medicine, January, 1916

TABLE OF TOTAL AND DIFFERENTIAL WHITE BLOOD CELL COUNTS

Date	W. B. C.	P. M. N.	P. M. B.	P. M. E.	Lymph.	L. M.	Myeloc.	Trans.	Unclass.
Feb. 5	9,000	61.8	0.25	0.25	28.6	8.4	....	0.8	....
Feb. 10*	.....	....	....	....	....	....	....	....	....
Feb. 15†	.....	.....	....	....	....	....	....	....	....
Feb. 26	6,700	38.0	....	....	13.6	8.4	....	40.0	....
March 4	.....	7.2	1.6	....	22.8	8.8	....	54.4	5.2
March 7	7,180	21.6	1.2	....	12.4	8.4	....	54.8	1.6
March 8‡	.....	.....	....	....	....	....	....	....	.....
March 11	13,280	63.0	....	....	4.0	5.0	4.0	20.0	4.0
March 12	18,280	60.4	....	....	2.4	8.0	2.0	27.2	
March 15‡	.....	.....	....	....	....	....	....	....	....
March 16	22,600	68.0	....	....	2.0	7.0	....	16.0	7.0
March 18	21,600	30.0	....	....	2.0	3.0	....	11.0	54.0
March 21	11,300	74.0	....	1.0	8.0	2.0	....	13.0	2.0
March 23	8,040	56.0	....	....	4.0	10.0	....	15.0	15.0
March 25	6,100	52.4	4.0	2.4	13.2	7.2	0.4	16.8	7.2
March 27	7,200	52.0	1.2	5.2	14.4	6.0	0.8	16.0	4.4
March 29	7,900	55.0	....	....	5.0	10.0	....	19.0	11.0
April 1	7,600	53.2	0.8	6.4	14.8	14.0	....	8.4	2.4
April 3	8,440	53.2	0.4	0.2	11.6	18.0	....	4.8	10.0

*0.3 gm. salvarsan intravenously.
†0.45 gm. salvarsan intravenously.
‡Pericardial friction heard.

the nucleus was a greenish-blue, showing no evidence of reticulation, and the protoplasm a faint pink with a very fine, indistinct, dust-like granulation of pinkish hue. The granulation which was so definite with Wilson's stain, was either absent with this stain or represented by a few faint pink granules which were never seen to overlie the nucleus. With Jenner's stain the protoplasm was a darker blue than with Wilson's, and the granulation, though constantly present, was not so striking. In none of these cells was a perinuclear clear zone noted. Using the "indophenolblau" reaction of Schultze,[13] oxydase granules were demonstrated in these cells in just as great abundance as in the polymorphonuclears. By means of staining the nucleus with saturated aqueous safranin before submitting the smears to the oxydase reaction, the different cells were definitely identified, although owing to the occasional overlying of the nucleus with oxydase granules the differential diagnosis between the transitionals and the polymorphonuclears was difficult in some instances.[14]

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13. Schultze, W.: Zur Differentialdiagnose der Leukämieen, München. med. Wchnschr., 1909, lvi, 167. See also Türk (Note 12), p. 202.

14. It was at first hoped that by staining the nucleus in connection with the oxydase reaction, a preparation might result that would admit of a microphotograph and thus make a permanent demonstration of transitional cells containing oxydase granules. The blue nuclear stains were of no help. Aqueous safranin, gentian-violet and cochineal were also tried, and of these safranin proved the most satisfactory, giving the desired intensity of staining in the shortest time. To save the oxydases from destruction, aqueous solutions used without a mordant were necessary, and under these conditions it required about eight minutes, depending somewhat on the age of the smear, to get a satisfactory staining of the nucleus with the saturated solution. Being an aqueous stain, it was rapidly dissolved out by the water in the dimethylparaphenylendiamin and alphanaphthol solutions used in the "indophenolblau" synthesis, so that when these solutions were allowed to remain on the smear long enough to result in a preparation of any permanency the red stain of the nucleus had become too faint to be photographed. On the other hand, if the smears were submitted to the oxydase reaction first, the eight minutes consumed in staining the nucleus rendered the preparation unsatisfactory by reason of the transient character of the oxydase reaction, which endured only about ten minutes. The technic finally adopted was as follows:

(a) Staining:
   1. Fix smears eight hours in formaldehyd vapor.
   2. Stain in saturated aqueous safranin solution for eight minutes.
   3. Wash quickly in water and dry immediately by careful blotting.

(b) Oxydase reaction: Put on slide.
   1. One drop of 1 per cent. aqueous solution of dimethylparaphenylendiamin, and
   2. One drop of freshly prepared 1 per cent. solution of alphanaphthol in 1 per cent. KOH dissolved by gentle heating.
   3. Mount previously stained smear in this and examine at once.

By this means a preparation of sufficient permanency of both the nuclear stain and oxydase granules was obtained to admit of satisfactory identification of the cells and a hasty differential count, but not enduring long enough to be photographed.

In order that any conclusions drawn from this case might be justified, strict adherence to the above characteristics was demanded of any cell counted with the transitionals. Any cell resembling a transitional to some extent but having a ground or oval nucleus, or having a somewhat irregular nucleus but lacking the customary intensity of granular staining with Wilson's stain, was classed with the large

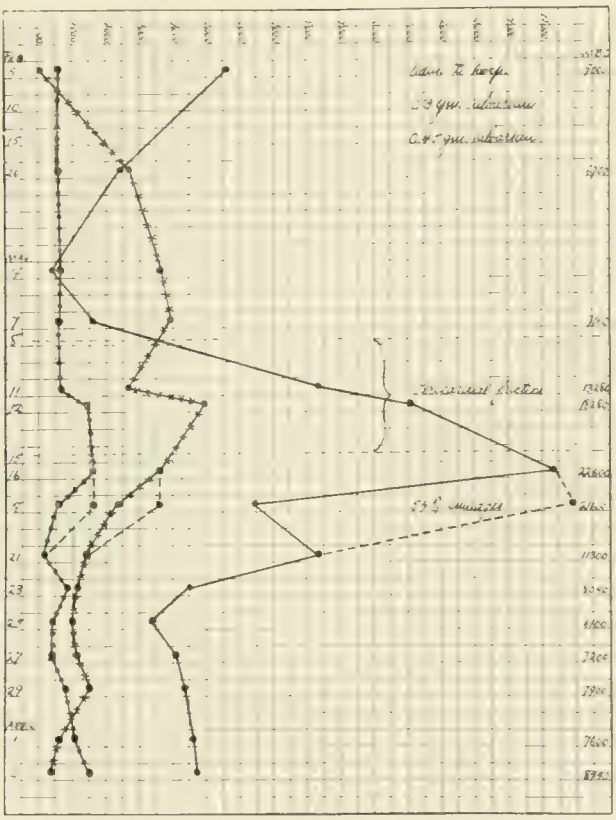

Fig. 2.—Curves of the polymorphonuclears, transitionals and large mononuclears in absolute number of cells per cubic millimeter of blood. The dotted lines represent the curves after the 54 per cent. unclassified cells noted March 18 had been proportionately allotted to each. Solid line above polymorphonuclears; line with dots, transitionals; line with crosses, large mononuclears.

mononuclears. Never, however, was a cell having a typically indented nucleus encountered which did not meet the qualifications in regard to granular staining, nor was a cell with the characteristic granules ever seen with a perfectly round or oval nucleus. The classification of those cells counted as lymphocytes, although not based on the size of the cell, was equally strict, only those with a deep blue-black

nucleus with Wilson's stain and a faint greenish-blue with Ehrlich's, and having a narrow strip of protoplasm, being counted in this group. The cells commonly accepted as large lymphocytes with a purple reticulated nucleus and abundant faint blue protoplasm, clear except for occasional azure granules with Wilson's stain, and a very faintly staining blue nucleus and pink protoplasm with Ehrlich's, and with a fairly constant perinuclear clear zone, were, together with the cells above described somewhat resembling the transitionals, included with the large mononuclears. Thus the group of large mononuclears was a composite one made up of at least two distinct types of cells, those resembling the transitionals preponderating. There was no transition stage between the true large lymphocyte and the cells resembling the transitionals but not exactly typical of them, although among these latter there were all gradations in point of intensity of granulation and shape of nucleus, from the most atypical to the true transitional. With Wilson's stain the more reticulated and irregular nucleus of the transitional, the neutrophilic granulations of its protoplasm and uniformly sharp edge, and the absence of the perinuclear clear zone, rendered confusion with the large lymphocyte out of the question; but when the nucleus was not typically indented and was overlain with a few neutrophilic granulations, as occasionally appeared, confusion with the myelocytes might be conceivable, particularly in faintly stained specimens. On the other hand, with Ehrlich's stain the faintly staining nucleus which characterized the transitional, and the scarcity and type of granulation which was never seen to overlie the nucleus, distinguished this cell from the myelocyte but rendered confusion with the large lymphocyte possible on casual observation, in those cells with a nucleus not typically indented.

THE REACTION

This patient with syphilitic aortitis, having no untoward symptoms after the administration of one dose of salvarsan and a severe reaction manifested by a dermatitis, hepatitis, nephritis and probably phlebitis after a second dose five days later, presented a case unique in the fact that there was also a great increase in the typical transitional cells of the blood. No similar case has been encountered in the literature following any kind of arsenic therapy. Naegeli[5] mentions a number of conditions in which a transitional cell increase has been described, the greatest noted being 17 per cent. in a case of lymph gland tuberculosis. Warfield[9] cites a fatal case of typhoid fever in which he counted 46 per cent. of these cells, but this is most unusual, and the constant increase noted by Bunting[10] in early Hodgkin's disease has never been more than 17.8 per cent. in his reported cases. The patient during the course of the illness also showed a pericarditis with

a typical friction rub and later with fluid, and a bilateral pleurisy with effusion, the former accompanied by an active leukocytosis.

It will be observed (Fig. 2) that the sharp rise of transitional cells was associated with a striking drop in the polymorphonuclears, but that the polymorphonuclear leukocytosis following later at the time of the pericarditis influenced the transitional curve only slightly. The characteristic precipitate descent of the polymorphonuclear curve after the subsidence of the acute process giving rise to the elevation, although synchronous with the falling curve of the transitionals, seems to be entirely without influence on it, the latter continuing the gradual descent noted both during the active polymorphonuclear leukocytosis and after the polymorphonuclear percentage had become approximately normal. Also, during the polymorphonuclear reaction, myelocytes were present in about the percentage to be expected, but at no time was a myeloblast observed, and at the end the blood was flooded with fragile forms incapable of being classified (see Table). These unclassified cells, by reference to the differential counts, seemed to be largely at the expense of the polymorphonuclears, and also to some extent of the transitionals and large mononuclears. However, proportionately allotted to these three groups of cells, they do not alter the curves materially (Fig. 2). The lymphocytes, through both the reaction of the transitional and polymorphonuclear elements, showed only the variations normally to be expected, and these variations were entirely independent of the other reactions (see Table). The curve of the composite group classed as large mononuclears and containing many cells greatly resembling the transitionals, being above the curve of the transitionals, as is normal, both before the reaction and after it had subsided, was constantly below it during the reaction, and except for a slight rise at the time of the leukocytosis, maintained an almost constant level (Fig. 2). At no time could enlargement of the spleen be made out by palpation or percussion and there was no variation in the slight general glandular enlargement noted on admission. No disturbance of the erythropoietic function occurred, as evidenced by the absence in the peripheral circulation of immature forms of red blood cells and the lack of polychromatophilia, etc.

DISCUSSION

The reaction of the blood in this case is interesting in reference to several views of the origin and status of the transitional cell. The initial fall of the polymorphonuclear curve coincident with the rise in the transitional seems at first sight to point to the transitional as one type of immature polymorphonuclear cell; but the subsequent sharp polymorphonuclear leukocytosis, associated as it was with the

presence of myelocytes and almost without influence on the transitionals, makes such a view untenable. Also this cell seems to be independent of the myeloblasts and myelocytes, for it is improbable that such an intense transitional crisis could have been present without one myeloblast being noted if they are related forms; and the presence of myelocytes only in connection with the polymorphonuclear leukocytosis affords additional evidence in support of this observation.

The lack of any relation between the number of transitionals and lymphocytes throughout the entire transitional reaction speaks against any association with the lymphoid system.

The reaction of this cell was also independent of any change in the percentage of the large mononuclears, although it bore, as above noted, great resemblance to some of the cells included in the large mononuclear group. This one large mononuclear cell suggesting on morphological grounds an intimate relation with the transitional, presented all stages between its most remote form and the typical cell counted with the transitionals, and was entirely distinct from all other cells of the blood. Yet even this cell, though possibly present in slightly increased numbers, did not vary enough to influence the almost constant level maintained by the total large mononuclear count. However, we feel in agreement with Ehrlich[3] and many others that there is a close relationship between these two cells, and incline to the belief of Naegeli[5] that they should be considered together as one cell group. The common opinion that of these two cells the one with the indented nucleus, the true transitional, is the older form and develops from the cell of the more regular nucleus, is directly opposed to the evidence available in this case. For, in normal blood, in which one might expect the older forms in greater numbers, the mononuclear percentage is greater than the transitional. When the system was specially stimulated, bringing out, as one is justified in supposing, the younger forms, the increase was almost exclusively in the true transitionals.

In regard to the origin of the cell, it is of interest that no enlargement of the spleen or superficial lymph glands could be made out. The rich content of oxydase granules in the transitional cells is strongly in favor of the bone marrow as the point of origin. The scope of this paper does not permit a discussion concerning the confidence to be placed in the demonstration of oxydase granules as a diagnostic point between cells of the lymphoid and myeloid systems, but most studies seem to indicate that the differentiation is definite.[15] In this case no oxydase granules could be demonstrated in the lymphocytes, but they

15. Gierke, E.: Die oxydierenden Zellfermente, München. med. Wchnschr., 1911, lviii, 2315.

were present in great abundance in all transitionals and polymorphonuclears. It has already been mentioned that in the "indophenolblau" preparations for the demonstration of oxydase granules the distinction between the polymorphonuclears and transitionals was difficult in some instances. This uncertainty did not exist in regard to all the cells, however, and when a blood specimen showing 7.2 per cent. polymorphonuclears and 54.4 per cent. transitionals (together 61.6 per cent.) as occurred in this case on March 4, contains oxydase granules in from 55 to 75 per cent. of the white cells in smears made the same day, the observation that all transitionals contain oxydase granules seems reliably controlled. The possible presence of phlebitis makes one strongly consider an endothelial origin for these cells, for a process intense enough later to cause a phlebitis might readily be conceived as capable of first producing proliferative changes in the intimal endothelium. This origin seems unlikely, however, for although oxydase granules have been observed in many cells of the body, including the endothelial when fresh tissue was used, Gierke[15] was unable to obtain them in any but the cells of the tear and thyroid glands, and in those of myeloid origin after formaldehyd fixation and alkaline solutions, as used in this case. In the endothelial and other body cells it has been quite definitely proved to be a peroxydase, distinct from an oxydase reaction and depending on the labile respiratory oxygenase destroyed or inactivated by the above technic, whereas the stabile oxydase of the myeloid cells, being more resistant, endures.[16]

SUMMARY

To summarize, the following observations were made on the reaction of the blood in this case.

1. That the productive center of the so-called transitional cell was capable of *specific* stimulation.

2. That there was a decrease in the polymorphonuclear coincident with an increase in the transitional cells but that this transitional reaction was not then or later accompanied by any immature cells of the polymorphonuclear system, and subsequent sharp polymorphonuclear leukocytosis, associated with a few myelocytes, was almost without influence on the number of transitionals.

3. That the transitional cells, in contrast to those of lymphoid and endothelial origin and in common with those of known myeloid origin, contained oxydase granules in great abundance after formaldehyd fixation and with alkaline solution of the reagents.

16. For discussion and references see Gierke, Note 15.

4. That there were no transition stages between any lymphocyte, large or small, and the transitional cell, and the specific stimulation of the transitionals did not influence the number of true lymphocytes in the blood.

5. That although one type of large mononuclear cell bears a striking morphological resemblance to the transitional, only the latter was increased under the stimulation which occurred, and the total number of those cells going to make up the large mononuclear group was uninfluenced by the transitional reaction.

CONCLUSIONS

While realizing that no definite statements can be made from the data afforded by a single case, in view of the unique opportunity offered by our case for study of the transitional cell we feel that the observations made strongly suggest the following conclusions:

1. That the so-called transitional cell is not an immature or degenerated form of any other cell type, but is an independent cell type in itself.

2. That the productive center of the transitional cell is closely related to that of the polymorphonuclear system, but is independent of it.

3. That the transitional is not an endothelial cell, bears no relation to the lymphocytes large or small, and is probably of myeloid origin.

4. That the one distinct type of large mononuclear closely resembling the transitional should probably be included with it to form an independent cell type; but that if there is any difference in the age of the cells of oval or indented nuclei, as seems likely, the cell with the indented nucleus—the typical transitional—should be considered the younger.

I take this opportunity to thank Dr. Walter A. Baetjer and Dr. Thomas P. Sprunt of the staff of the Clinical Laboratory for their kindly interest and many helpful suggestions in the study of this case.

ADAMS-STOKES SYNDROME — PERSISTENT BRADYCARDIA INVOLVING BOTH AURICLES AND VENTRICLES. REMARKABLE PROLONGATION OF THE As-Vs INTERVAL *

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The patient, Mrs. X., aged about 55, came under my observation on the 27th of April, 1913, in consultation with my friend Dr. Hardin of Washington.

At thirteen the patient had had scarlet fever, and six months later diphtheria, followed by more or less extensive paralysis. In other respects she had been a healthy woman and had had several children. For ten or twelve years, however, there had been some shortness of breath on exertion, and for eight months, frequent bleeding from the nose. For two months she had had peculiar periods of dizziness in which it had been noticed that her pulse was slow and irregular. Two weeks before she had had a sudden attack characterized by loss of consciousness and repeated slight convulsive seizures. Immediately after the attack the pulse was very slow, about 18 to the minute, and fairly regular. On the morning preceding the attack it had been 44; since the attack it had ranged between 28 and 35.

Examination showed a fairly healthy looking woman, lying on her back in bed. The pulse was regular, 36 to the minute. On inspection of the neck, by a rather poor light, there was a well-marked impulse in the jugular with each beat of the pulse, together with a second impulse, occurring at a point about midway between each beat. A satisfactory analysis of the jugular undulation was impossible because of the dimness of the light.

The heart was slightly enlarged; the sounds were clear throughout. There was heard, however, between each regular beat, a slight but yet distinctly audible sound. This occurred constantly about midway between the regular heart sounds, and had the general character of the sound which one commonly hears in association with the auricular contraction in heart block.

We were inclined to regard the condition as one of heart block with a 2:1 rhythm. Tracings were taken which are reproduced in Plates I and II. These tracings show, as may be seen, a bradycardia with an average ventricular rate of 33.7 to the minute. There is but

* Submitted for publication Sept. 8, 1915.

one auricular wave to each ventricular beat. That is, there is a like slowing of both chambers with *a-c* periods of unusual length. In twenty-three consecutive beats the *a-c* period ranges from 0.65 to 0.82 second in length, averaging 0.73 second.

The first, and most natural thought that came to one's mind was that this must, after all, be a 2 : 1 rhythm, and that, on careful examination, an elevation corresponding to a second auricular beat might be discovered somewhere on the tracing. And, indeed, rough measurements suggested, at first, that the sometimes prominent notch on the katacrotic limb of the *c* wave might possibly represent the beginning of a second *a* wave. For the differences in the periods separating the obvious *a* waves from the katacrotic notches on the succeeding *c* waves, and those between the latter and the next prominent *a* waves, were so slight that on first study of the tracings, we were inclined to accept this explanation.

A more careful study, however, shows that the consecutive *a* waves and the katacrotic notches on the *c* waves are not equidistant one from another, the distance from a given *a* wave to the succeeding notch being almost always slightly greater than that from the notch to the following *a* wave. Moreover, the *a* wave is a large, clearly defined elevation and the wave following the notch but slight and sometimes ill-defined. One is therefore obliged to assume that the condition is one of bradycardia involving both auricles and ventricles; and further, the remarkably constant relation between the *a* and *c* waves suggests that the chambers respond to a like impulse conveyed along the usual paths, with a remarkable delay in transmission. The impulses visible in the neck, and the sounds audible between the ventricular contraction were clearly associated with auricular systole.

Five weeks later, on the third of June, the patient came to Baltimore for further polygraphic and electrocardiographic study. At this time she appeared to be in excellent condition. The pulse was 36 to the minute; the blood pressure was high, by estimate about 180. In the jugular the same slight impulse was visible between arterial beats, and with the arterial beat no definite presystolic impulse could be seen. The radials were not palpable. The point of maximum cardiac impulse was palpable in the fifth space, about 10 cm. from the median line, the dulness extending about 3 cm. to the right of the sternum. There was no retro-sternal dulness. At the apex there was a slight systolic murmur following the first sound, and between beats a soft, short sound was heard. This was loudest at about the juncture of the sixth rib and the sternum on the left, but was audible all over the cardiac area. The liver was palpable on deep inspiration, descending just below the costal margin.

Electrocardiographic records were first taken, after which the patient who seemed a little tired and short of breath, walked slowly up two flights of stairs where further polygraphic tracings were made. The electrocardiograms are reproduced in Plates III, IV and V. They show a bradycardia involving both auricle and ventricle, similar to that recorded in the polygraphic tracing five weeks before.

In Lead I (Plate III) the rate of the pulse is 35.9 to the minute, and the average P-R interval reaches the remarkable figure of 0.68 + second. The beats follow one another at regular intervals, and beyond the long P-R periods there is little striking about the record. The P waves follow one another at regular periods and there is no sign at any point of another P complex interfering with R or T elevations.

In Lead II (Plate IV), however, there are several variations from the usual relation and character of the P and R complexes. In this film the rate of the heart's action is 35.4 to the minute, and the average P-R time, 0.70 + second.

The R wave is inverted and has a rather flat summit with a notch in the middle. The P wave is large and triangular in form. The auricular beats are separated by a period usually varying from 1.6 to 1.7 seconds. At one point (*w*) after the ninth R wave on the record and 1.3 + seconds after the preceding P wave, there appears a small inverted deflection which has the general complex of a P. This is followed in 0.88 + second at *x*, by an erect P, somewhat smaller than the regular auricular complex, and this in turn is succeeded after 0.23 second at *y*, by an R deflection which differs distinctly in form from the ordinary R in the tracing. The next P follows at *z* after a shorter period than usual—1.08 + seconds—but occurs but little in advance of the time at which it would ordinarily have been due, and has its usual complex. Following this slightly precocious P elevation there is an unusually long P-R interval—0.88 + second—and the next P complex follows after a delay of nearly 0.2 second beyond the ordinary P-P interval. The P complexes, excepting the two at the points *w* and *x*, are quite similar in form. The R complexes occur at practically regular intervals throughout and at but one point (*y*) do they show any variation from their usual appearance.

In Lead III (Plate V) in which, unfortunately, but a short film was made, the heart's rate was 35.5 per minute and the P-R interval averages 0.69. There is nothing striking about the appearance of this film. The R and T waves are inverted. The P waves are smaller than in Lead II, of much the same general appearance as in Lead I.

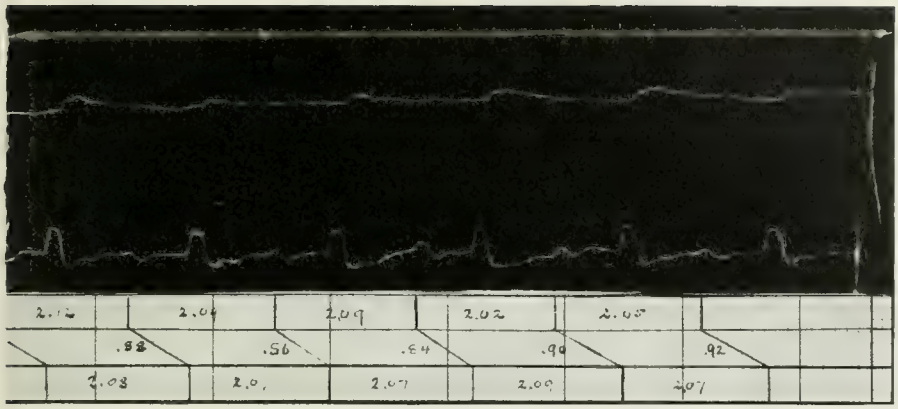
The next record was taken with the Mackenzie polygraph (Plate VI). The patient seemed a little nervous and tired and had walked up two flights of stairs. The pulse rate had become slower—31.3 to

the minute. The average *a-c* interval was 0.79 + second. The general appearance of the tracing was exactly similar to that taken on April 23, but at two points slight irregularities were noted, associated, I think, with swallowing or some other movement. At the first of these points (*x*) regular *a* and *c* elevations can be made out, although the former is immediately preceded by an unaccountable wave. The succeeding *a* is separated from the next *c* by an unusually long period. At the second point (*y*) there is an elevation preceding the *v* wave, and the latter is followed by that which appears to be an *a* occurring at a remarkably precocious period, and separated from the succeeding *c* by a very long space of time. Although no special notes were made on the tracings at the time when they were taken, the irregularities at *x* were, I think, dependent on movements of some sort, for I remember distinctly that although the tracings were rather carefully studied, no serious irregularity was noticed at the time. It may be that the elevation at *z* represents a precocious auricular systole similar to those on Lead II of the electrocardiogram, but I am disposed to regard it as an artefact. Nothing similar was observed on the rest of a fairly long tracing.

Lastly, carotid and jugular tracings were taken with a Verdin polygraph (Plate VII). There was some difficulty in obtaining a satisfactory record. The patient became rather nervous and tired. The rate of the pulse is here 28.8 to the minute, while the *a-c* interval varies from 0.81 to 0.97 second, reaching the remarkable average length of 0.886. Excepting for the slower rate of the pulse, and the remarkably long As-Vs interval, the tracing differs in no essential from those made with the Mackenzie instrument.

How are we to explain these remarkable records? Are we to assume that we are dealing with an instance of complete heart block with idio-ventricular rhythm, or are we to fancy that the stimulus for each contraction has developed at the normal point and that we have before us an example of simultaneous slowing of all chambers of the heart with an auriculo-ventricular conduction time amounting in some instances nearly, if not actually, to one second, and with a P-R interval which averages between 0.6 and 0.8 second?

In favor of the former assumption we might regard the rate of the heart, 29 to 35 to the minute, almost exactly that of ordinary idio-ventricular rhythm, as well as the circumstance that in Lead II of the electrocardiogram where, at one point, two atypical auricular complexes occur, the ventricular rhythm remains essentially unaltered. But strongly against such an explanation seems to me the circumstance that in a series of tracings taken after an interval of five weeks, the relations of auricular and ventricular contractions remain almost the same. It is hardly conceivable that at such varying periods of time,



0. Pulse, 28.8. *a-c* time, .886 sec.

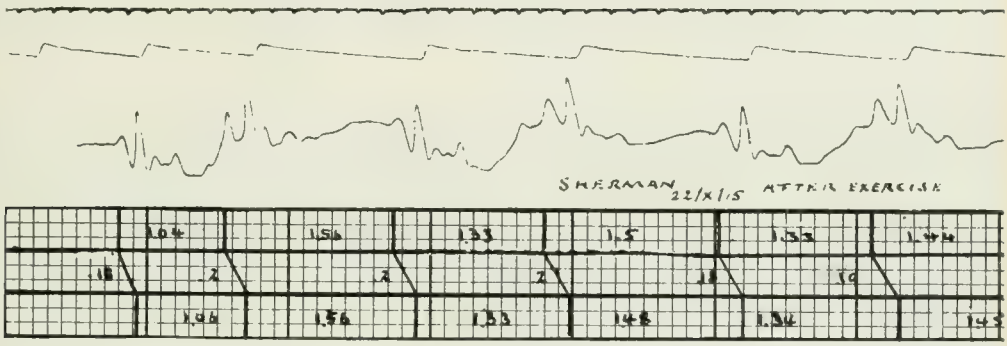


Plate IX.—S. 22/x/13. After exercise. Rate, 43.

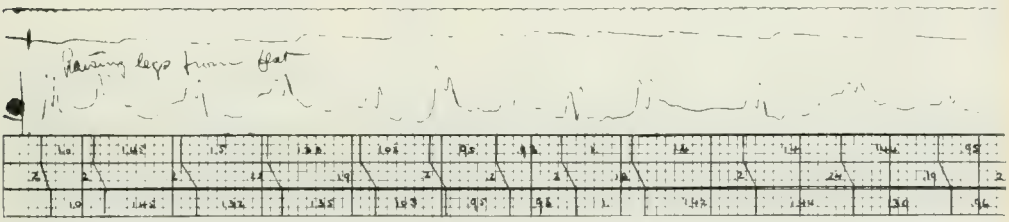


Plate XI.—S. 25/x/10. Exercise. Rate, 49.

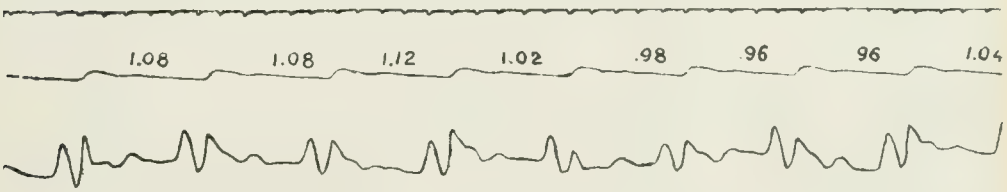


Plate XIII.—S. 27/x/10. After atropine, 0.002 (

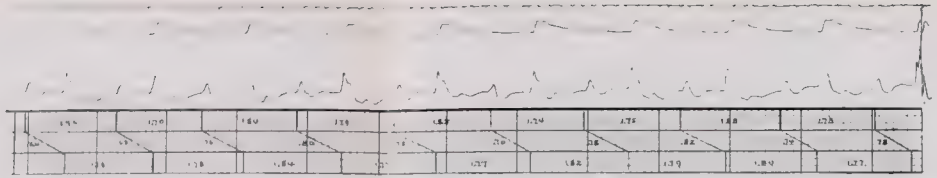


Plate I. Mr. . . 3. Pulse 335 . . mm. 768 . .

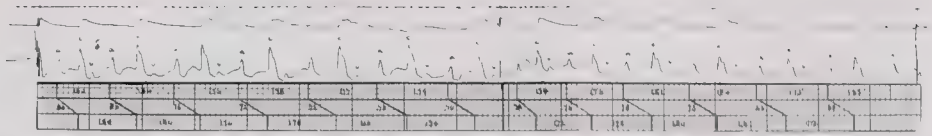


Plate I. Mrs. X. 2. . . 13. Pulse 84 . . .

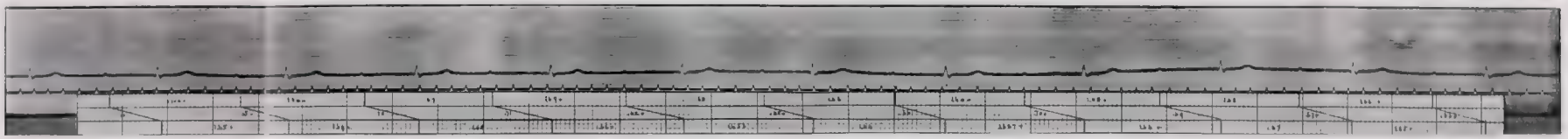


Plate III. Mrs. X. Dec. 13. Lead I. Pulse 350. P-R period .08 + sec.

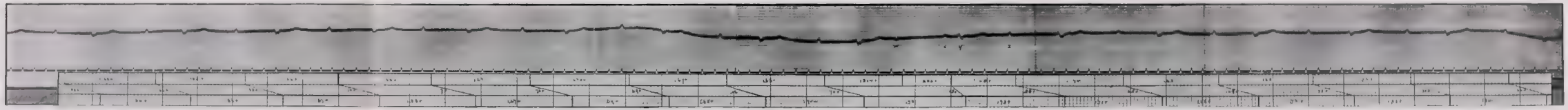


Plate IV. Mrs. X. . . 13. Lead II. Pulse 354. P-R period .7 sec.

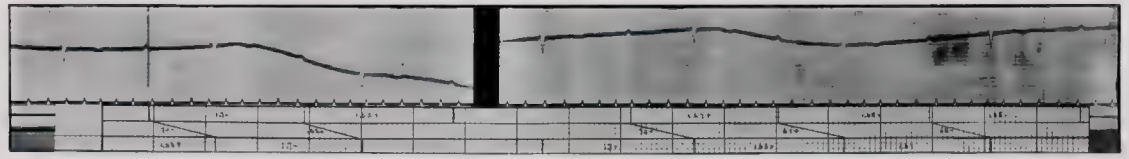


Plate V. Mrs. X. Dec. 13. Lead III. Pulse 355. P-R period .07 sec.

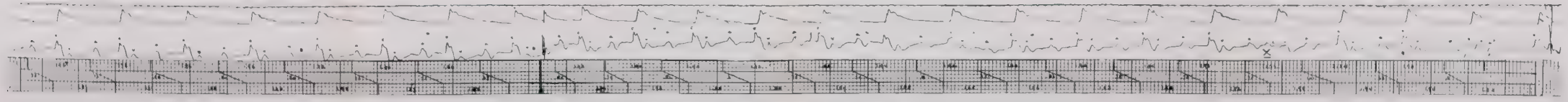


Plate VI. Mrs. X. . . 13. Pulse rate 313. P-R period. .79 +

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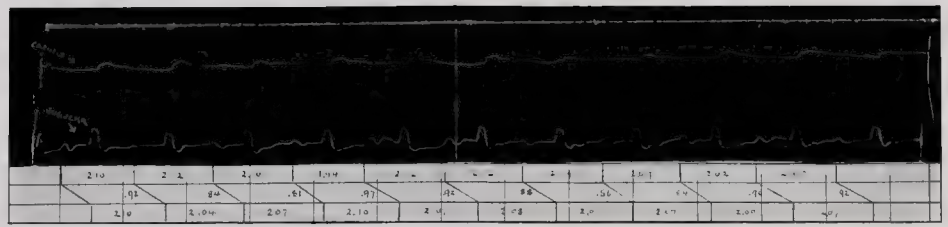


Plate VII Mrs X 3/xi/11 Pulse 288 duration time, 886 sec

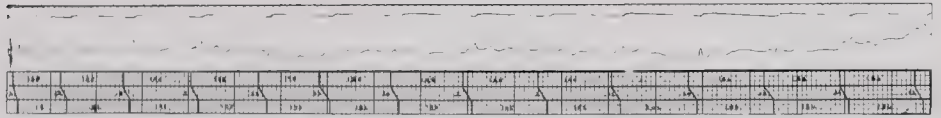


Plate VIII S 22/x/10 Pulse 317 duration time 21 sec

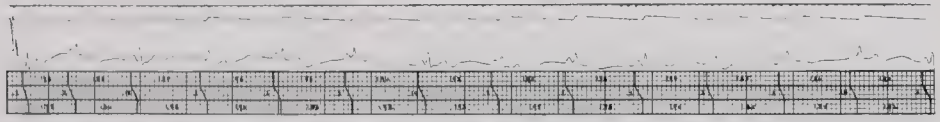


Plate X S 22/x/10 Continuation of tracing IX after a short pause to read just receiving cap over jugular Rate 318 duration time, 19 + sec

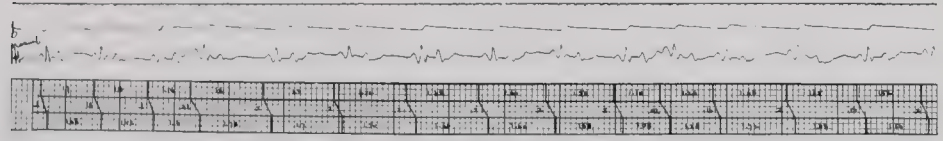


Plate XII—S 27/x/10 Before administration of atropine Rate 39.2 duration time, 19 sec

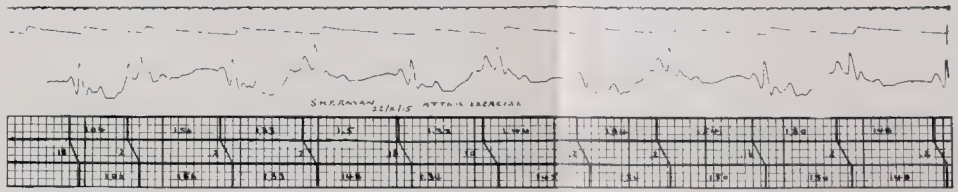


Plate IX S 22/x/13 After exercise Rate 43 [illegible] 19 + sec

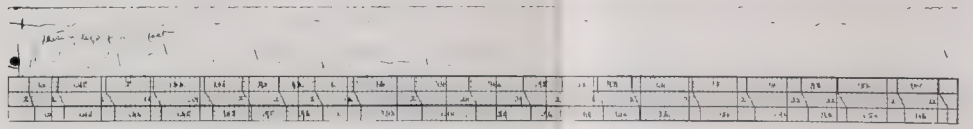


Plate XI—S 25/x/10 Exercise Rate 40 [illegible] 20 +

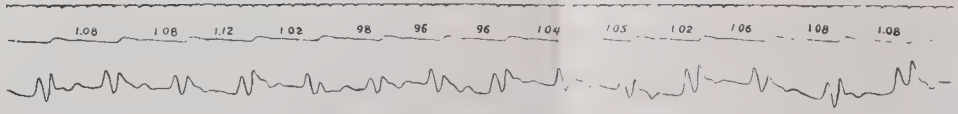
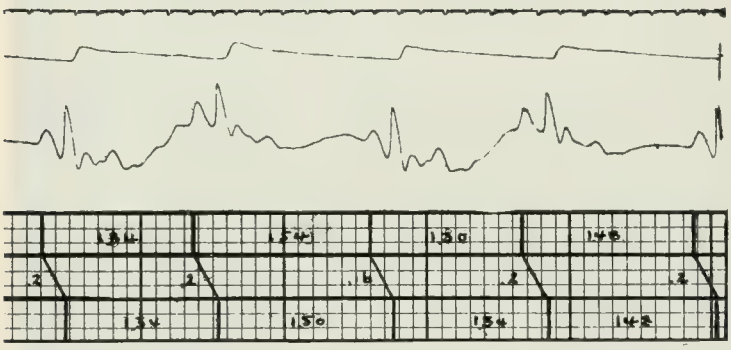
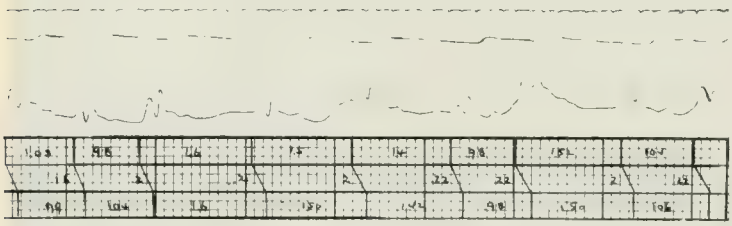


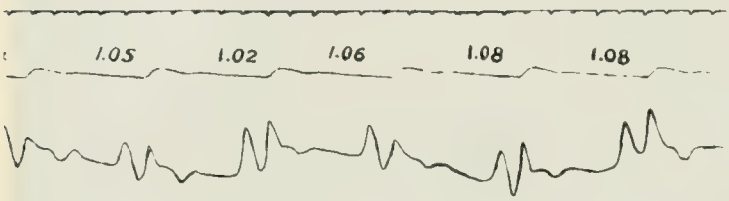
Plate XIII S 27/x/10 After atropine 0.002 per kg Rate 57.6



2. *a-c* time, .19 + sec.



3. *a-c* time, .20 +



gr. 1/30). Rate, 57.6.

and in so many tracings, the relation in time between the *a* and *c* waves and the P and R complexes should have been so constant unless auricular and ventricular action were controlled by common stimuli.

Another argument in favor of this assumption would seem to be the character of the R wave in the electrocardiogram. This does not present the diphasic excursions commonly seen with idio-ventricular rhythm, but has rather more the appearance of a complex dependent on a stimulus carried from above along the bundle.

How may one explain the events on Lead II of the electrocardiogram?

The first inverted P complex (*w*) is probably an auricular extrasystole.

How are we to explain the abnormal complexes associated with the following P and R elevations? It would not seem probable that a P-R interval so short as 0.23 second could represent a true conduction time when, throughout the rest of the film, the P-R interval is never shorter than 0.64 second, unless it be that we fancy that the P elevation here is an extra systole arising in the node or bundle. In extra systoles arising in junctional tissues, the P and R elevations are usually, it is true, much more closely associated. But might not the delay in this instance reasonably be explained by the anomalous conditions which are accountable for the remarkable length of the P-R interval during the regular cardiac action? The suggestion that the P wave at *x* is an extra systole is supported by the slight variation in its complex, which has already been mentioned.

Following this extra systole, the next regular stimulus represented by the P elevation at *z*, occurring after a shorter period than usual and meeting with an exhausted bundle, is followed by an unusually long P-R interval—0.88 second.

The variation in the R complex at *y* suggests, however, another possible explanation. Might it not be that this complex represents an idio-ventricular contraction quite unassociated with the impulse responsible for the preceding P? The sequence of events then might be as follows: A precocious auricular systole at *w* in a heart in which, owing to disease of the bundle, the P-R time is greatly delayed, finds the bundle refractory and is blocked. At *x* there occurs a second auricular contraction at a period fully 0.4 second later than that at which the regular auricular contraction should have occurred. Owing, however, to the long continued bradycardia at a rate close to that of ordinary idio-ventricular rythm, the heart is continually on the threshold, as it were, of idio-ventricular impulse formation. And indeed, after a delay slightly longer than usual, such an idio-ventricular contraction

occurs at *y*, at a period considerably in advance of the time when the stimulus responsible for the auricular contraction at *x* might have been expected to produce a ventricular response.

An exceptionally interesting feature of these tracings is the great prolongation of the As-Vs interval in the last tracing, in which the average *a-c* period was 0.886. On the whole we see a gradual slowing of the pulse from beginning to end of the records taken June 3, a diminution in the rate from 35.9 to the minute at the beginning of the electrocardiographic records to 28.8 to the minute in the one successful tracing which was obtained with the Verdin instrument; this course of events suggests the possibility that physical exhaustion may have resulted in slowing of the cardiac rhythm and delay in the conduction time.

I have, unfortunately, been unable to see the patient since June, 1913. In July of that year she had two attacks of vertigo with unconsciousness and convulsions lasting several minutes. At the time of the attack the pulse was slow and irregular; immediately afterwards it varied from 28 to 50. Dr. Hardin writes me:

"In June, 1914, she had three more severe convulsions; one at three o'clock in the morning, another six hours later and another early the following morning. Following these convulsions there was continuous and violent vertigo, markedly increased by raising her head from the pillow, and lasting for eight days.

"The next and last attack was on the 17th of February, 1915, when she fell in her bathroom and was unconscious for some time following. I have never seen her in one of these convulsions and have been unable to secure any definite data from any of those who have witnessed the attacks. Her pulse has varied from 28 to 44 when we have seen her during the past winter and she complains almost continually of mild vertigo and a sense of confusion and uncertainty in her head."

We have waited nearly two years before presenting these records in the hope that it might be possible to continue our observations. Unfortunately, the patient's family have consistently refused to allow further polygraphic or electrocardiographic studies.

It was early felt that it might be well to try the effect of large doses of atropine but unfortunately the patient shows an unusual idiosyncrasy towards the drug. Dr. Hardin writes:

"The minutest dose poisons at once. I have tried it several times when she in unsuspecting. I have seen $\frac{1}{500}$ of a grain (0.00013) of atropine and also one drop of the tincture of belladonna flush her face and dilate the pupils so that she cannot see at all, produce great restlessness, insomnia and excitement for hours and hours."

Clinically the course of events was typically that of an Adams-Stokes syndrome, and it would seem from the history as if at the time of the syncopal and convulsive attacks, there may well have been long

intermissions in the pulse. On the two occasions in which we have been able to study the patient, however, there has been no actual auriculo-ventricular dissociation, but a slowing of both auricles and ventricles to a rate of from 28 to 35, about that of the ordinary idioventricular rhythm, with a great prolongation of the As-Vs interval. The remarkable As-Vs interval, as well as the rate of the pulse might lead one to suspect a true dissociation, and the circumstance that in Lead II of the electrocardiogram, despite irregular auricular contractions at one point, the ventricle continues its regular rate, might support such an hypothesis.

On the other hand, the constancy of the As and Vs relations, which remained unchanged for an interval of five weeks, would be almost inexplicable unless we assume that the contractions of both chambers are governed by a common impulse. Again, the R complexes are of such a character as to lead one to believe that they are dependent on a supraventricular stimulus. The one serious objection to this assumption, that based on the regularity of the ventricular rate at the time of the auricular extrasystoles in Lead II of the electrocardiogram, would not seem to be serious if we regard the ventricular complex at *g* as a single idioventricular contraction arising after a very slight delay, in a heart muscle the rate of contraction of which has been for a long time so slow that it has been continually on the threshold of idioventricular stimulus formation—an hypothesis which is supported by the character of the complex.

The unprecedented length of the As-Vs interval—*a-c* periods averaging over 0.7 second and reaching at some points nearly, if not quite, one second in duration—P-R intervals often exceeding 0.7 second, can hardly be used as an argument against our interpretation of the manifestations. For although we are unaware that As-Vs periods so long as this have been previously observed, yet Griffith and Cohn,[1] and Peabody and the writer[2] have recorded instances in which the *a-c* interval has amounted to from 0.5 to 0.6 second.

What may be the pathological basis for such remarkable functional manifestations? From the data at hand, it is obvious that one can but speculate. The great lengthening of the As-Vs interval and the history of the syncopal and eclamptic manifestations would suggest disease of the *a-v* bundle. But how shall we explain the slow auricular rate? Despite the general regularity of the auricular beats and the

1. Griffith, T. W., and Cohn, A. E.: Remarks on the Study of a Case Showing a Greatly Lengthened a-c Interval with Attacks of Partial and Complete Heart-Block, with an Investigation of the Underlying Pathological Conditions, Quart. Jour. of Med., 1910, iii, 126-151.

2. Thayer, W. S., and Peabody, F. W.: A Study of Two Cases of Adams-Stokes Syndrome with Heart-Block, The Archives Int. Med., 1911, vii, 289-347.

persistence of the phenomenon, abnormal vagus influences cannot wholly be ruled out. One might fancy that there were changes which had resulted in a 2:1 sino-auricular block, but with the information at hand this can only be advanced as an hypothesis without supporting evidence.

Instances of permanent slowing of the auricular action to a rate below 40 with regularity, are by no means common. Such an instance I had the opportunity to study several years ago.

S., aged 30, a civil engineer, consulted me on the 21st of October, 1910, complaining of nausea, dizziness and "sinking spells." He had been a rather heavy smoker, consuming as many, sometimes, as fifteen cigars a day. He had worked very hard at his profession. He had been married four years and had two children.

He had had no serious illnesses in childhood and had never been subject to tonsillitis. As a child he had not been allowed to exercise very vigorously because, as he said, he had not "grown up to his heart." At college he took up rowing, but was generally taken out of the boat for some reason or other before the competitions. He had never suffered from palpitation, dyspnœa or coughing.

For five years his physician had noticed that his pulse was slow, ranging usually between 44 and 52. Early in May, five months before I saw him, while under an unusual stress of work, he had an attack of vertigo on the golf links which obliged him to lie down on the ground. After about two minutes he was able to arise and finish the game. A week or two later there was a similar attack while sitting in a chair at dinner, so that he fell forward onto the table. This was followed by several like attacks at intervals of about ten days, and in the first week in July he had a very severe paroxysm in the street car. The attack lasted while the car was passing about three blocks; he did not fall from his seat. After these attacks he was very weak and felt that he must lie down.

At the time of the attack in the street car he was seen by an excellent physician who found a ventricular rate of 32 to the minute, and what appeared to be a double venous impulse in the neck, suggesting a heart block with a 2:1 rhythm. He then went to the mountains, spending some days quite at rest. At this time his family physician found his pulse from 32 to 36. In twenty-four hours the pulse had risen to 42. A few days later, on the 15th of July, he had a nervous attack associated with a sense of sinking, feeling very weak, as he expressed it, "as if my blood were all going out." His physician states that his pulse was again 32.

Although there was no history or evidence of lues, he was treated with mercury and iodide of potassium with apparent improvement until August 1, when he had another "sinking spell" which was repeated again two weeks later. At these times the pulse ranged from 28 to 32. The patient suffered also from a feeling of nausea in the morning and felt rather dizzy, but was inclined himself to feel that his dizziness was nervous. From the 15th of August he gradually improved and now, October 21, feels perfectly well.

In my consulting room the patient appeared a healthy man. Nothing abnormal beyond the cardiac conditions was found. The pulse was between 30 and 35, essentially regular. Now and then a beat occurred at a period a little earlier than it might have been expected, but was followed by no compensatory pause. Inspection of the neck showed a normal venous undulation, all three waves being plainly visible. The patient was a well nourished man over 6 feet tall. The heart was a little large, the impulse easily palpable in the fifth space, 11.5 cm. from the median line, slightly within

the mammillary line; relative cardiac dulness, 3.3 cm. to the right of the mid-sternum. The first sound was prolonged and followed by a slight, indefinite systolic murmur, heard in the axilla and rather louder over the base; the second sounds were clear and of normal relative intensity. The murmur was less intense in the erect posture, and barely audible at the apex; not heard in the back. The heart was normally mobile; occasionally, as the patient was lying on the left side, a third sound could be heard.

Polygraphic tracings with the Mackenzie instrument showed marked bradycardia involving both chambers of the heart; no extra auricular beats were to be seen; the *a-c* time was normal. The patient entered the hospital for study. A radiographic examination of the chest revealed nothing abnormal.

The urine and blood showed no abnormalities. The Wassermann test gave a negative result. Radiographic examination of the chest showed nothing unusual.

While lying quietly in bed the pulse varied in rate from 28 to 35. The rhythm, though essentially regular, showed, at times, variations consisting of occasional precocious beats suggesting sometimes extrasystoles. These beats were not, however, followed by compensatory pauses, (Plate XII) and, on the whole, were suggestive of an ordinary sinus arrhythmia.

Respiration was associated with the normal changes in rate, and exercise and emotion accelerated the pulse in the usual manner, but rarely, if ever, to a rate above 50 to the minute. The slight irregularities in rhythm were somewhat more evident after exercise. It is not impossible as suggested by my colleague, Dr. Bridgman, that this exaggerated irregularity is associated with respiration.

Numerous polygraphic tracings showed little beyond the bradycardia.

The tracing reproduced in Plate VIII, taken when the patient was at rest, shows an essentially regular pulse at the rate of 31.7, with a normal *a-c-v* sequence. The *a-c* interval is a shade long, 0.21 + second. In the next tracing taken a little later, after exercise (Plate IX), the rate of the heart is 43.2. The *a-c* interval averages 0.19 + second. There is an interesting alternation in the length of the intersystolic periods. This phenomenon was, however, not observed at any other time in our study of the patient. In the following tracing (Plate X), taken after a short pause to adjust the receiving cup over the jugular, the pulse has already fallen to 31.8 and this alternation is no longer evident, while in later records (Plate XI), taken after exercise, no such alternation is seen, although the rhythm shows considerable irregularity.

Atropine 0.0011 (gr. $\frac{1}{60}$) and 0.0016 (gr. $\frac{1}{40}$) administered subcutaneously, produced little or no effect on the heart's action. After 0.0022 (gr. $\frac{1}{30}$) the pulse rate increased gradually to 60. A polygraphic tracing continued for over half an hour after the injection, showed no abnormalities (Plates XII and XIII). It was, unfortunately, impossible to obtain electrocardiographic records as the instrument was out of order.

Since this period the patient has seemed physically well, but the pulse has always remained at a rate between 30 and 40 while at rest. I last saw the patient about two years ago as he was about to go on the table for an appendectomy. The pulse at this time was 32, and the venous undulation in his neck, perfectly normal. He passed through the operation without ill effect. His physician, Dr. E. P. Carter of Cleveland, who has studied the patient carefully, and confirmed these observations, writes (July, 1915):

"S. is very well, active and busy. His pulse . . . when last taken by me in May, was 39 to the minute. Polygraphic records have never shown any increase in his *a-c* interval. . . . he has had no attacks of dizziness since you saw him."

Here then we have the history of an individual the rate of whose cardiac action has apparently diminished gradually through a period of years, until, five years ago, it reached a permanent rate of but little over 30 when at rest, a rate which has been maintained since that time.

At one period, five years ago, after excesses in work and tobacco, there were several attacks of vertigo and nausea. The pulse, at these times, was a little over 30 and regular. With improvement under rest there was, however, no change in the rate of the heart's action, and the pulse remains today, when the patient appears to be in perfect health, at essentially the same rate. In polygraphic tracings the *a-c* interval is normal and beyond slight sinus irregularities in rhythm which are increased on exercise, nothing of note is revealed.

What are we to regard as the cause of the bradycardia?

It is hardly possible to ascribe it to vagus influences, for experiment shows that the vagus influences are essentially normal. Respiration is followed by the usual variations in rhythm and atropine produces its usual effect, *proportionately, however, to the initial cardiac rate.*

One is hardly justified, in the present state of our knowledge, in assuming the possibility of a persistent sino-auricular block—an hypothesis against which one might advance further the essential regularity of the pulse through such long periods of time, as well as the gradual increase in rate, without irregularity following atropine. One would fancy that we are here concerned with an essentially slow stimulus formation, with a so-called sinus bradycardia, a bradycardia depending on chronotropic influences solely.

But in what do such influences consist? Is the condition to be regarded as pathological or only as anomalous?

These are questions which must be answered by time and by further study.

To what were the phenomena of vertigo and nausea due? The physicians who observed the patient at the time of these attacks were at first under the impression that a wave possibly indicating an auricular contraction, was to be seen in the jugular between each regular beat. If this observation of his physicians was correctly interpreted we must assume that, at this time, there was a true heart block—a 2 : 1 rhythm. The absence of prolongation of the *a-c* interval is no proof that such a condition may not have existed. One would, however, hardly expect vertigo with a regular pulse of thirty and above, unless this slow pulse followed suddenly on a rate considerably more rapid —unless, say, it were a question of a sudden halving of the pulse rate. May this have occurred at the time of these attacks?

Such an hypothesis might be advanced to explain the phenomena observed in this patient. I have seen a similar sequence of events in an individual with chronic myocardial disease, whose pulse when at rest, was in the sixties. Any effort, such, for instance, as sitting up and down several times in bed, was followed by a slight increase in the auricular rate with the dropping out of every other ventricular

contraction. After a few moments' rest the regular As-Vs sequence was resumed. At no time was there any prolongation of the *a-c* interval.

Experimentally, however, in the present case, it was impossible to reproduce any such phenomenon by exercise or atropine, and even with vigorous exercise the pulse rate was never observed at a point above sixty. It is a question whether the apparent double auricular impulse in the jugular may not, perhaps, have been simulated by the large and very evident *v* wave; indeed such now is the opinion of the physician who has had the patient constantly under observation.

On the whole the writer is inclined to agree with him and to doubt whether any actual auriculo-ventricular dissociation has ever occurred in this patient. He is disposed to regard the vertigo and nausea as the results of a generally overwrought mental and physical state in an individual who might well be predisposed to such symptoms because of his anomalously slow heart action.

To what this remarkable bradycardia may be ascribed is a question which, as has been said, cannot definitely be answered.

The phenomena observed in this patient are similar to those described in Mrs. X. mainly in that in both there is a striking bradycardia involving both chambers of the heart.

In the former patient (Mrs. X.) both the history and the results of physical examination revealed evidences of grave disease of the *a-v* bundle—Adams-Stokes syndrome with extreme slowing and irregularity of the pulse and remarkable prolongation of the As-Vs period. In the second patient, however, there was no lengthening of the As-Vs interval and, despite the history of vertigo and nausea, there was no evidence that auriculo-ventricular dissociation had ever occurred. Indeed, the symptoms pointed, rather, to an unexplained sinus bradycardia.

SUMMARY

The history is presented of a woman who for two years and a half has had occasional syncopal and eclamptic attacks with extreme bradycardia.

Between these periods the pulse is regular, averaging (in rate) but little over 30 to the minute.

Polygraphic and electrocardiographic study reveals a synchronous slowing of both auricles and ventricles with prolongation of the As-Vs interval to a period longer than has hitherto been reported. In polygraphic tracings the *a-c* interval amounts to from 0.7 to 1.0 second; in electrocardiograms the P-R time is often over 0.7 second.

The history of syncopal and eclamptic attacks with great slowing and irregularity of the pulse, as well as the prolonged As-Vs interval

observed in our studies, justify a diagnosis of disease of the auriculo-ventricular bundle. The cause of the auricular bradycardia which would appear to depend on an essential anomaly of impulse formation, is not clear.

A second case of apparently essential sinus bradycardia is reported.

This subject is a seemingly healthy man now 35 years of age. The heart rate for at least five years, has been between 30 and 40 when the patient is at rest. There is no prolongation of the As-Vs interval. Exercise, deep breathing, atropine have their usual effects on the heart's rhythm and rate, but proportionately to the initial cardiac rate.

Attacks of vertigo and nausea occurred five years ago but there is no evidence that these were associated with auriculo-ventricular dissociation. The patient remains in apparently good health despite his persistent bradycardia.

I am indebted to my colleague, Dr. Bond, for the electrocardiograms in Case 1.

Plates I, II and VI were, owing to an unfortunate mistake, reinforced by hand over the original tracing before reproduction, a circumstance which accounts for certain irregularities in the line of the tracing.

THE TYPHOIDIN QUOTIENT

QUANTITATIVE STUDIES OF THE CUTANEOUS TEST OF TYPHOID IMMUNITY *

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In view of the uncertainty about the duration of immunity conferred by antityphoid inoculation and the occasional occurrence of typhoid fever among those recently vaccinated, it is highly desirable to have a test which will indicate the existence or absence of immunity and if possible also the degree of immunity. Gay and Force[1] have discussed the heretofore unsatisfactory efforts to utilize agglutination and other biologic reactions for this purpose, and have described promising experiments with a cutaneous typhoidin test.

The technic used in this investigation was described by Gay and Force[1] and is similar to the Pirquet tuberculin test. It consists in making two circular abrasions without drawing blood by rotating a chisel with a 2.5 mm. blade. "Typhoidin" was applied to one spot and the control application to the other. The preparation of killed typhoid bacilli in liquid culture medium having been found by Gay and Claypole[2] to deteriorate on standing, the same was dried and ground and a small particle of the powder rubbed into the abraded area with a sterile toothpick.[3] The control application consisted of a similar preparation of the culture medium (glycerin-bouillon) without the typhoid organisms. The reactions were examined after about twenty-four hours. In order to minimize the personal factor in interpreting these results and to obtain figures as objective as possible, the reactions were not recorded as "positive" or "negative," but only the diameters of the areolas were put down. Usually at least a small blush could be observed about both the control and the typhoidin spots, and the great-

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* From the Departments of Medicine and of Pathology and Bacteriology, University of California.

1. Gay, F. P., and Force, J. N.: A Skin Reaction Indicative of Immunity Against Typhoid Fever, The Archives Int. Med., 1914, xiii, 471.

2. Gay, F. P., and Claypole, Edith M.: An Experimental Study of Methods of Prophylactic Immunization Against Typhoid Fever, The Archives Int. Med., 1914, xiv, 671.

3. It is still too early to state definitely the potency and keeping qualities of the dried typhoidin. Further experiments on this question are to be undertaken in the Department of Pathology and Bacteriology. The typhoidin here employed had been prepared one year previously.

est diameter of each was measured. For this purpose a machinist's vernier gage was used, which reads to 0.1 mm., and which enables the observer to set the instrument to the required measurement without seeing the result until afterwards. Papule formation was disregarded in the analysis, since it is not subject to the same objective interpretation and only occurs when there is a well-marked areola.

Because the areolas never have absolutely sharp edges, the subjective element in gaging the two spots is not removed by these measurements, though it is undoubtedly materially lessened. It is also quite evident, however, that as cutaneous diagnostic tests have been used, the greatest play of judgment has occurred, not in estimating the comparative size of the areolas, but in the subsequent decision as to whether or not the comparison warrants reporting the test as "negative," "positive," "weakly positive," etc. The actual measurement of the areolas makes it possible by reporting merely the relation between two quantities to eliminate entirely this latter uncertainty.

The most obvious ways of expressing mathematically this relationship are to combine either the two surface areas of the areolas or the two diameters to form either a difference or a quotient. Without going into the theory of local allergic phenomena, it may fairly be considered probable that the intensity of the biologic mechanisms responsible for dilatation of small blood vessels is related to the distance from the inoculated points to which hyperemia extends (radii or diameters of the areolas) rather than to the number of arterioles involved (surface areas). As to the mathematical relationship to be used for connecting the diameters — if the control reactions were always the same, it would be proper to suppose that the intensity of the biologic reaction to the typhoidin was more or less proportional to the excess of the test-areola diameter over that of the control spot, i. e., that the difference between the two diameters should be used as a basis for comparison. But the fact that there is considerable individual variation in the reactions due to the trauma of the chisel itself, with or without the control application, suggests that there is a corresponding variability in the extra extension of the hyperemia by the typhoidin, independent of any immunity mechanism. If this is true, it follows that the ratio of one diameter to the other is a better index of the relative intensity of the reaction. This ratio (diameter of the typhoidin spot divided by that of the control) may be termed the *typhoidin quotient*. Whatever its merits, it will be realized that the process of obtaining the typhoidin quotient is exactly what is attempted subconsciously whenever one interprets such reactions by simple inspection. For example, if in a given case the control diameter is 2 mm. and that of the test spot 4 mm. the reaction will invariably be judged

positive, whereas with the same or even greater difference in the diameters the test will be considered negative or doubtful if the areolas measure 10 or 12 mm. The parallelism will be noted to the well known Weber-Fechner psychological law governing sensations.

Considerable experimental evidence will of course be required before it can be stated that these quotients indicate relative degrees of protection against typhoid fever, though in a general way this may be expected to prove true. What is urged is that it is possible, not only

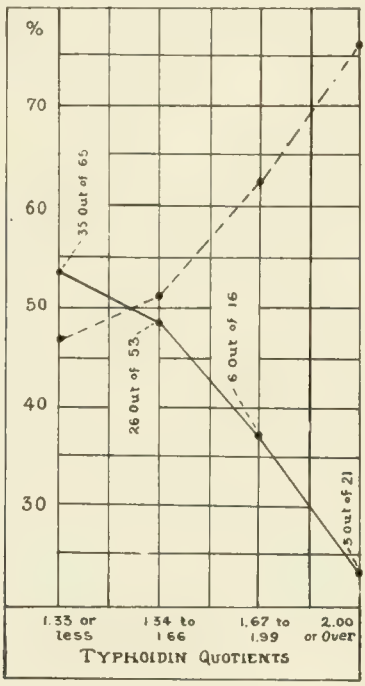

Fig. 1.—Relation of the typhoidin quotient to the previous history of typhoid fever or vaccination. Dotted line indicates those supposed to be immune, solid line the nonimmunes. Numbers at bottom show the four classes according to typhoidin quotients, figures at left show percentages in each group.

in typhoidin but also in tuberculin and other related cutaneous tests, to eliminate much of the observers' personal element by reducing to figures the process of "reading" the reactions. In view of this increased objectiveness and the way thus opened for quantitative analyses, it is felt that at least for purposes of record and reporting, these quotients deserve to come into general use. Clinical records of cutaneous reactions to be complete should give both of the diameters and their decimal quotient.

The diameter of the chisel has not been deducted from the diameters of the two areolas before computing the quotient, for the reason that this quantity in both dividend and divisor keeps the quotient within reasonable bounds (otherwise it would approach infinity when the control reaction was slight or absent) and in no way interferes with its usefulness. Chisels should of course be of uniform width.

The subjects consisted of 162 individuals, fifty-eight women and 104 men, who were mostly from among the staff, students, nurses and employees of the University of California Medical Department and Hospital, and from the departments of dentistry and pharmacy. Most of them were young adults, a few were middle aged.

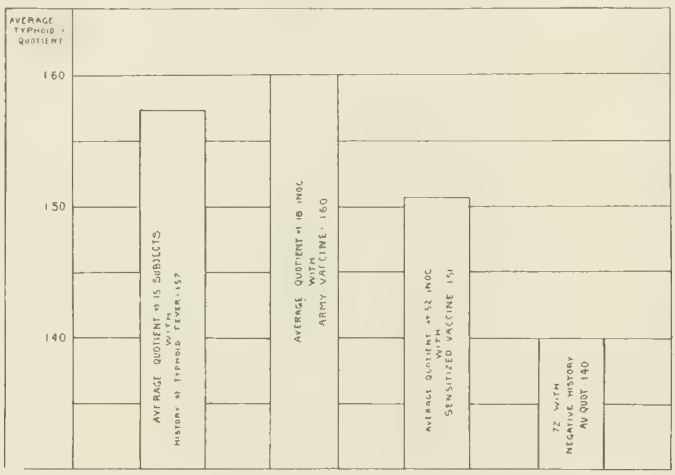
AVERAGE TYPHOID QUOTIENT
160
150
140
AVERAGE QUOTIENT OF 15 SUBJECTS WITH HISTORY OF TYPHOID FEVER-1.57
AVERAGE QUOTIENT OF 18 INOC WITH ARMY VACCINE- 1.60
AVERAGE QUOTIENT OF 52 INOC WITH SENSITIZED VACCINE 1.51
72 WITH NEGATIVE HISTORY AV QUOT 1.40

Fig. 2.—Average of typhoidin quotients of immunes, those who have had typhoid fever, those who have had army vaccine, and those who have had sensitized vaccine.

RELATION OF THE TYPHOIDIN QUOTIENT TO THE HISTORY OF PREVIOUS TYPHOID FEVER OR VACCINATION

For showing this relation the cases were divided into four groups according to their typhoidin quotients. The first group consists of sixty-five persons with typhoidin quotients 1.33 or less; the second of fifty-three with quotients from 1.34 to 1.66; the third of sixteen with quotients from 1.66 to 1.99; and the fourth group of twenty-one with typhoidin quotients of 2 or over. The solid line of Figure 1 shows the percentage of supposedly nonimmunes in each of these groups. The numbers at the left indicate percentages, those at the bottom the groups according to typhoidin quotients. In connection with each dot indicating a percentage the number of cases in the group is given and the number of nonimmunes, that is, the figures from which the corresponding percentage is obtained. The dotted line shows the percent-

ages of those in the different groups who have been vaccinated against typhoid, or who have had typhoid fever. From the figure it will be seen for example, that for a subject with a typhoidin quotient of from one to one and two-thirds, the chances that he belongs to the immune or nonimmune group are about equal; while if his typhoidin areola is at least twice the diameter of the control (quotient 2 or over) the chances are about three out of four that he has had typhoid fever or vaccine.

The vaccinations were all from one-half to two and one-half years previous to the test; the cases of typhoid fever dated back from a few weeks to twenty-five years. Those who had had typhoid fever or different kinds of antityphoid vaccination were not numerous enough in the different groups to warrant separate comparisons.

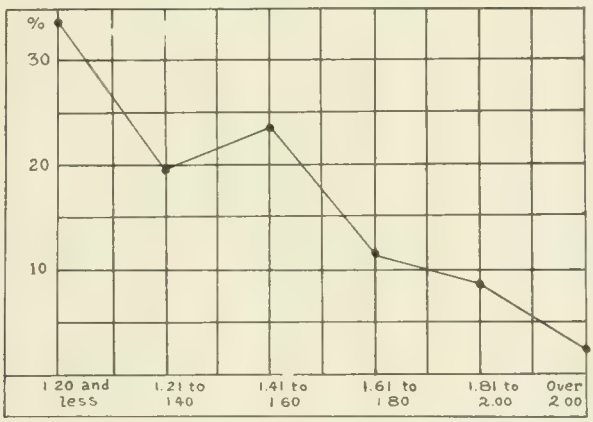

Fig. 3.—Variation in typhoidin quotients among supposedly nonimmunes, that is persons with "negative" history. Numbers at bottom indicate groups separated according to typhoidin quotients, at left percentages of the total number of the nonimmunes (seventy-two).

Figure 2, however, shows the relation of typhoidin quotients from a slightly different point of view, the average quotients being charted separately of those with negative history (72 cases), those who had had typhoid fever (15 cases), those who had had army vaccine (18 cases), and those who had received the sensitized vaccine of Gay and Claypole[2] (52 cases).

Those with history of typhoid fever and those who have had army vaccine have nearly the same average quotients, about 1.60; those with negative history have the lowest average, 1.40; while those who had received sensitized vaccine have an intermediate average. The lower average quotient for the sensitized vaccine group is notwithstanding the fact that the majority of these subjects were vaccinated from one to two years ago, while most of those who had had army vaccine were vaccinated two and one-half years ago.

The seventy-two who denied having had antityphoid vaccination or typhoid fever (in questioning the subjects care was taken to rule out so far as possible unrecognized typhoid) had typhoidin quotients ranging from 0.75 to 2.50 and averaging 1.40. The distribution of these values is shown in Figure 3.

A certain percentage of individuals with negative history have had unrecognized typhoid fever. Sawyer[4] and Gay and Claypole[2] have shown that these cases may be considerably more numerous than has been commonly supposed; and they may account for a certain number of the high quotients in persons with negative history. Figure 3 shows, however, that in the vast majority of the negative cases the reaction is definitely more to the typhoidin than to the control application, so that the reaction can hardly be called even "probably positive" unless the quotient is well over 1.50. It may be added that Figure 3 showing the wide variation of values in the "negative history" group is fairly representative of conditions in the different groups of supposedly immunes.

A few of the low quotients in persons who give a history of having had typhoid fever may be accounted for by mistaken diagnosis, but probably most of them should be considered as failures of the test. One physician with quotient of 1.00 had typhoid fever with positive Widal three years previously. A hospital patient with a quotient of 1.11 had had proved typhoid fever, which subsided about seven weeks previously—possibly his typhoidin reaction would be stronger at a later date.

Gay and Force in some instances found typhoidin reactions appearing as early as six hours and early fading. This I believe to have been true in some of the cases in this series and possibly a few of the failures may be thus accounted for; but the six-hour observations which it was possible to make were so few that it was thought better to omit them entirely from the analysis.

From Figure 3 it will also be seen that it is not the occasional case that departs far from the general average, but that there is a very general wide scattering; so that the probable error in any given case is large. This has been determined to be 0.22 by the use of the following formula:[5]

$$\text{Probable error of a single observation} = \pm 0.6745 \sqrt{\frac{S}{n-1}}$$

when S = the sum of the squares of all the quotient differences from the mean, and n = the number in the series. That is, in any given

4. Sawyer, Wilbur A.: Ninety-Three Persons Infected by a Typhoid Carrier at a Public Dinner, Jour. Am. Med. Assn., 1914, lxiii, 1537.

5. Stewart and Haldane: Elementary Practical Physics, Edit. 2, p. 267.

case in this group the chances are even that the quotient will differ from 1.40 (the general average) by more or by less than 0.22.

The probable error in the average quotient itself is 0.045 as determined by the formula

$$\text{Probable error of the mean of the whole} = \pm 0.6745 \sqrt{\frac{S}{n\,(n-1)}}$$

That is, the chances are even that the true average quotient for nonimmunes, supposing it to be based on thousands of observations, would lie within or without the limits 1.355 and 1.445. As stated above, this amount of variation in the quotient values among nonimmunes is representative of the typhoidin quotient variability among the immunes.

CONCLUSIONS

1. The use of typhoidin, tuberculin and other "quotients" in interpreting cutaneous diagnostic reactions is urged, for the reason that objectiveness is thus increased and quantitative analyses made possible.

2. In individual cases the test as here used has a high probable error and is therefore not conclusive.

3. It has a neutral significance when after twenty-four hours the typhoidin quotient is in the region of 1.40 to 1.50, that is, when the typhoidin spot is about one and one-half times the diameter of the control.

4. When the quotient is considerably above 1.50, immunity to typhoid fever is suggested.

5. When it is considerably below this value nonimmunity is suggested.

When applied by statistical methods to groups of cases it may, however, be capable of much more definite interpretation as a qualitative index of typhoid immunity; since the general averages in this series of cases as well as in those previously reported by Gay and Force[1] show well-marked *average* differences in reaction between the immune and nonimmune.

It is suggested, furthermore, that when applied in this way to sufficiently large groups of cases, the typhoidin quotient may prove useful as a quantitative index of typhoid immunity.

For valuable assistance I am indebted to Dr. Ethel M. Watters and for criticisms and suggestions to my colleague, Dr. James L. Whitney.

THE SPLENIC PATHOLOGY OF PERNICIOUS ANEMIA AND ALLIED CONDITIONS

A DUODENAL METHOD OF ESTIMATING HEMOLYSIS *

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MINNEAPOLIS

The spleen is dismissed with brevity in textbooks on pathology. Current medical literature fails to reveal a serious study of its histology, normal and pathologic.

In a close association with Professor Dr. Hans Eppinger and his co-workers in the von Noorden clinic during the past year, I had opportunity to study not only the microscopic material obtained from that clinic, but in addition, many specimens loaned by Banti and Weidenreich.

The second part of this paper will deal with a study of the duodenal contents in a series of nineteen cases with a view of presenting a relatively simple yet accurate method of measuring the pleochromie and urobilinocholie so characteristic of the above splenic pathology.

PART I

From Biermer's first definite and popular clinical conception of pernicious anemia in 1868 to Ehrlich's hematological studies in 1892, a host of workers contributed to the elucidation and confusion of this fatal malady. It was Syllaba in 1904 who first clearly recognized and properly emphasized the icteric feature of pernicious anemia.

In a demonstration of the splenic pathology of pernicious anemia, hemolytic icterus and hypertrophic cirrhosis, before the Society for Internal Medicine in Vienna in November, 1913, Eppinger gave the profession for the first time the results of many months of labor, suggesting what certainly amounted to an innovation, splenectomy for the first and last of the above conditions.

Prefacing his study of the pathologic picture in that most difficult and little understood organ with a survey of the normal histology as taught by Weidenreich, he pointed out the necessity of a proper schematic conception, to-wit:

Following the blood vessels as they traverse the trabecular partition, we find when a lumen of 0.2 mm. is reached the artery leaves

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the wall and penetrates a follicle. It is now known as the central artery, and is characterized by a fairly heavy wall. From this, laterally, spring numerous follicle capillaries of very delicate structure and first demonstrated in serial section by Weidenreich. These lose their identity in the margin of the follicle and the so-called pulp area. Following the central artery out from the follicle we have the pulp artery with its characteristic spindle-celled intima. This last portion now ends its existence as an artery in the so-called "Hulsen arteries" phase with its Schwaiger-Seidel wall. Via a capillary, phase communication is established with the venous sinus. This latter is generally accepted as practically a closed space, making up the bulk of the red pulp of the spleen. Lined with "*Stabzellen*," with their prominent nuclei, the basement membrane is probably very elastic, supported by ring fibers. The sinus empties by means of a vein, leaving the pulp and following the trabecular wall.

Experimental injection of the spleen via the artery seldom permits of filling of the sinuses. On the contrary, the injected material is seen to leave the artery in the peripheral zone of the follicle or the outlying pulp parenchyma. Foreign corpuscles introduced intravenously come to lie in this region.

A survey of a section from a spleen removed at operation in a case of pernicious anemia shows, contrary to what the organ findings in general would prepare one for, a great richness in blood, this richness limiting itself predominatingly to the pulp areas—the sinuses being comparatively empty.

All varieties of erythrocytes can be seen, and not infrequently is met the picture of engulfed cells in the macrophages in the sense of Dominici. A diapedesis of erythrocytes into the sinus is seen.

It now becomes pertinent to inquire as to the manner in which these great masses of erythrocytes get into the pulp area.

Physiologically, the central artery has thick walls. In a section through this artery in a spleen of pernicious anemia the arterial wall is, however, of enormous thickness. Characteristic is the media with its masses of inlaid hyalin. Prepared with Mallory's stain, this appears as a heavy mass of red-brown tint. In certain sections, filling the arterial wall almost to the point of complete obliteration, this degeneration feature extends out far into the pulp phase of the artery.

It is Eppinger's conception that this lumen-obliterating pathology works a hindrance to the normal blood stream in so far as to force an unusual amount of blood to travel via the capillaries directly into the pulp area. Once in contact with the connective tissue spaces of the pulp area, the erythrocyte is marked for destruction. It is a fact that the efferent artery of the follicle has a physiologic lumen rhythm,

controlled by the nerve supply, looking to the regulation of hemolysis, for Thoma found that he could best inject the sinuses via the artery with coloring matter when he added atropin. Contrary to the conception of Addis, hemolysis occurring to the extent of allowing the detection of free hemoglobin in the spleen is rare; and whether engulfed by the phagocytic endothelial cells or not, the actual hemolysis occurs in the Kupffer cells of the liver perenchyma.

In one of my illustrations from a case of hemolytic icterus is seen, as in pernicious anemia, a pulp area packed with erythrocytes, with the sinus space relatively empty.

In hypertrophic cirrhosis, so-called, the spleen presents to a less exquisite degree this hyperemia of the pulp and, on the contrary, a marked degree of fibroadenie. This is properly regarded as an expression of a corrective tendency, for early in the life history of this type of cirrhosis during the acute catarrhal icterus attacks, the spleen presents a similar picture of acute hypersplenie.

PART II

In animal experimentation the administration of a simple large dose of an hemolytic agent produces a passing change only in the total blood picture, so quickly does the vicarious activity of the bone marrow come into play. It is therefore not improbable that in human pathology the hemolytic factor is missed entirely until the activity of the bone marrow shows signs of failure.

Up to the present our safest means of arriving at some comprehension of the severity of the process has been the degree of immaturity of the elements in the blood stream. We have no adequate means of arriving at a valuation of the blood-destroying factor, and yet the blood-picture must of necessity be regarded as the sum total of the blood-destroying factor set against the blood-building factor. The fundamental factor is the former. The worth of this basic hemolytic factor we are now in a position to estimate in a quantitative study of the blood-derived pigment.

In the haunts of the liver-spleen circulation the erythrocyte is physiologically made *hors de combat*. The resulting hematin is metabolated into bilirubin in the liver parenchyma cell. In the bowel tract this latter is reduced after bacterial fashion into urobilinogen. A portion of this is lost in the stool, partly as the mother substance above and partly as urobilin. The greater part is returned to the liver via the portal system, there to be synthesized into bilirubin and possibly hemoglobin.

Eppinger, therefore, in his earlier work foresaw that the estimation of the urobilin stool output must yield a very valuable measure

of the hemolytic factor. Applying the method evolved by Charmas he found normally an excretion per diem of 0.12 to 0.15 gm. In cases of hemolytic icterus he postulated a higher total, but he was scarcely prepared for the enormous values found, 1.75 to 3.95 gm.; namely, from fourteen to twenty-three times the normal. In pernicious anemia 0.24 to 1.14 or two and a half to seven times normal values. In anemia secondary to carcinoma, on the contrary, the values were around 0.012 or 1/10 normal. In cases of hemolytic icterus and pernicious anemia, following splenectomy he found in both instances a reduction to from 0.015 to 0.062 gm. per diem. It was this similarity in hemolytic values as measured by the stool urobilin output that led Eppinger to have splenectomy performed in pernicious anemia, and to study more closely the pathology of the spleen so recovered. For it may be remarked in passing that for microscopic study the surgically removed spleen, secured by tying off the artery first, is of value only as against the postmortem spleen where the final bone marrow exhaustion and depleting hemorrhages too completely overshadow the primary fulminating blood-destroying process.

Working under Eppinger, Bondi began in 1913 a study of the blood derived pigments in duodenal contents removed with Einhorn's duodenal tube, applying the Charmas method for a measure of the urobilinocholie. He argued that such estimations made, so to speak, at the very fountain-head of the pigment source must of necessity be less influenced by many factors working variations on the stool and urine output. In general he found values running parallel with the stool findings, but, owing to the involved and not entirely accurate method of Charmas, he contented himself in most instances with a simple statement of the gross character of the bile and a qualitative test for urobilin and urobiliogen.

Wilbur and Addis[1] in a very comprehensive and valuable study of the hemolytic values as found in the urinary and stool output came to the conclusion that of the two the latter gave promise of yielding the most fruitful help. Using the spectroscopic method, it is their distinction to have emphasized the superiority of this method and the necessity of determining the value of urobilin and urobilinogen by the same standard, at the same time, in order to arrive at a correct worth of these very labile pigments.

Stimulated by close association with the workers of the von Noorden clinic during the greater part of 1914 into the conviction that our knowledge of that fatal malady, pernicious anemia, was on the threshold of elucidation, the author on his return applied himself to the problem of adapting to the duodenal contents some method

1. Wilbur and Addis: The Archives Int. Med., 1914, xiii, 235.

of estimating the bile pigments other than the time-consuming one of Charmas.

In the method of Wilbur and Addis as applied to the urine the author found a simple, rapid and fairly accurate method for measuring the urobilinocholie. Since, however, the first expression of hemolysis is the pleochromie, it is of prime importance in the duodenal contents to estimate also, with some degree of accuracy, the bilirubin content. This is accomplished by the Huppert method, in so far as to allow of expressing the values secured, properly, as +, ++ or +++.

TECHNIC

Relative to the technic of securing the duodenal contents, a little needs to be said in the present state of diversity of methods. Contrary to the idea of certain workers, including Crohn and Rehfuss, it is not only not necessary to give food to secure secretion but distinctly undesirable. The mechanical stimulation of the metal bulb is all sufficient for secretory stimulation, and has the great advantage of enabling one to deal with undiluted, unmodified secretions. In the second place the capillary-sized tube is to be preferred over one of larger caliber, owing to the help secured by capillarity. At no time is it necessary or wise to apply suction. In the third place the time element is in favor of the above simple method in that it enables the securing of the contents in a remarkably short space of time — the average time consumed in arriving in the duodenum being twenty-five minutes.

The patient is prepared by allowing him to go food-free for twelve hours — an empty stomach is imperative. With the patient sitting, the bulb is placed on the posterior tongue, a swallow or two of water taken, and with puckered lips a sucking action is alternated with intervals of swallowing, teaching the patient at the same time the value of deep breathing to control nausea. Once the bulb has passed the cricoid ring level the disagreeable features are over. The further progress of the tube is largely beyond the control of patient and operator in that peristaltic action pulls the tube onward and the patient simply gives way to the tense tube by supplying more. On 80 cm. being reached the patient is placed on his right side close to the edge of the bed with hips elevated from 10 to 12 inches. This makes the pars pylorica the most dependent portion of the stomach. In from ten to thirty-five minutes the tube will have been carried into the duodenum and it now stands at 90 cm. If at any time the flow appears to be checked for an abnormally long time a few cubic centimeters of water are forced into it to dislodge the occluding particles. During this period it is necessary to test with red litmus the contents as it appears at the orifice of the tube each few minutes, for neither the required depth of tube nor a proper bile-colored contents are a sufficient guide as to the position of the tube. *It must react alkaline to litmus.* This alkaline-reacting portion is segregated, and after sufficient is secured for the work in hand the tube is removed and the contents immediately made use of in the following manner:

1. Gross Appearance.—Color: This is of prime importance and four distinct shades are found. The chocolate-yellow secretion is characteristic of pleochromie. It always yields a +++ value bilirubin. The normal yellow bile may vary in opacity according as it is rich in bile acids admixed with hydrochloric acid. This is by many erroneously regarded as mucus. The lighter shade of yellow is significant of a duodenal secretion poor in biliary pigment, just as the colorless secretion is proof of absence of pigment.

2. Bilirubin.—To 10 c.c. of duodenal contents are added 10 c.c. of an alkaline solution of calcium chlorid. After vigorous shaking this is filtered. The pre-

cipitate is dissolved under gentle heat in 10 c.c. of acid alcohol and the resulting green solution concentrated to a given volume. By colorimetric comparison with a standard green solution the quantity is indicated as +, ++, or +++.

3. Urobilin and Urobilinogen.—To 10 c.c. of duodenal contents are added 10 c.c. of Schlesinger's solution, the whole thoroughly shaken and allowed to filter. The filtrate should be inclined to be slightly alkaline; if not, a drop or two of dilute ammonia solution are added. The filtrate will in the presence of urobilin show a more or less pronounced green opalescence. To 10 c.c. of this filtrate are added 1 c.c. of Ehrlich's benzaldehyd solution.[2] In the presence of urobilinogen a red color will develop. This is allowed to stand in a dark place for fifteen minutes, when it is subjected to a spectroscope study for the values of both urobilin and urobilinogen. The acid character of Ehrlich's solution enhances the absorption bands of both these pigments many fold, the urobilinogen band being a very dense, narrow one in the yellow and the urobilin a wide one covering all of the blue into the green, the acid shifting the latter to the blue side.

The above solution is read in a graduate, and dilutions made with 95 per cent. alcohol, until a point is reached for each pigment where the absorption band will have disappeared at a fixed median position of the aperture, to again reappear with two revolutions of the aperture towards closure.[3] The number

In developing this method as applied to the duodenal contents it would appear that bilirubin being so concentrated would present a practical difficulty in that it gives a diffuse absorption of the spectrum. Wilbur and Addis, working with the products of gallbladder fistulae, etc., made use of fullers' earth to remove bilirubin. I found that it did so but that it also removed especially urobilin. If the original 10 c.c. are well shaken with Schlesinger's solution before filtering, practically all of the bilirubin is removed, the retained quantity causing no error or inconvenience owing to the fact that the end-stages are read in a highly diluted medium where any slight diffuse absorption of the spectrum no longer operates.

That the above simple method is quite as accurate as one first removing bilirubin was established by comparing the values thus secured with those arrived at in which bilirubin was removed by the Huppert method prior to adding Schlesinger's solution.

After having arrived at a safe technic, the following studies were made, covering a total of nineteen cases during a period of five months:

MATERIAL EXAMINED

Case 1.—J. A., Dec. 15, 1914. Diagnosis: pernicious anemia. Blood: count, 1,000,000; hemoglobin, 22; index, 1.1; macrocytes; macroblasts. Duodenal tube introduced, 9:30. Opalescent; debris considerable; after fifteen minutes yellow tinge; negative to Congo throughout; total quantity of gastric secretion 60 c.c. Total achylia; microscopic, spirals, polymorphonuclear cells with nuclei retained.

Entered duodenum at 9:50. Tube removed at 11:30. Total quantity 70 c.c. Very dark chocolate yellow color; alkaline to litmus; microscopic negative. Bilirubin, +++; urobilin, +++; urobilinogen,++. Feces: guaiac negative. Urine: bilirubin, 0; urobilin, +.

2. Paradimethylaminobenzaldehyd, 2 gm.; acid hydrochloric, 15 c.c.; aq. dest., 15 c.c.

3. Kirchhoff and Bunsen, large model, page 12.

of dilutions required for each element multiplied by twenty (5 c.c. of the original duodenal contents) will be the dilution value per 100 c.c. Following the basis used by Wilbur and Addis, I have reduced the value to the scale of 1,000 c.c.

Dec. 30, 1914. Blood: count, 930,000; hemoglobin, 25; index, 1.3; macrocytes, etc. Duodenal tube introduced, 9:00. Opalescent; much debris; after ten minutes yellow; negative to Congo; total 35 c.c.; total achylia; microscopic, same as previous examination.

Duodenum entered at 9:20. Tube removed at 11:00. Total quantity, 100 c.c. Exceedingly dark, alkaline to litmus; microscopic, negative. Bilirubin, + + +; urobilin, 3,000; urobilinogen, 3,000. Total, 6,000. Urine: bilirubin, 0; urobilin, 1,200.

Jan. 1, 1915: Blood: count, 2,000,000; hemoglobin, 45; index, 1.2; resistance, 0.45-0.30. Duodenal tube introduced 9:35. Less debris; after ten minutes light yellow; negative to Congo; total 50 c.c. Tube removed 10:40. Dark yellow. Bilirubin, + + +; urobilin, 2,000; urobilinogen, 3,600. Total, 5,600.

Feb. 25, 1915. Blood: count, 2,400,000; hemoglobin, 54; index, 1.1; no blasts. Duodenal tube introduced 9:20. Total 25 c.c. Duodenum entered at 9:45. Tube removed 10:40. Total 45 c.c. Less dark.. Bilirubin, + + +; urobilin, 1,600; urobilinogen, 2,000. Total, 3,600.

March 20, 1915. Blood: count, 2,600,000; hemoglobin, 60. Patient up in wheel chair. Duodenal tube introduced 9:35. Ditto. Total, 40 c.c. Duodenum entered at 9:55. Tube removed at 10:50. Total, 40 c.c. Dark yellow. Bilirubin, + + +; urobilin, 1,400; urobilinogen, 1,600. Total, 3,000.

Case 2.—E. P. Dec. 26, 1914. Diagnosis: secondary anemia.[4] Blood: count, 2,000,000; hemoglobin, 30; index, 75; anisocytosis and poikilocytosis. Duodenal tube introduced 9:30. Milky secretion; much debris; after fifteen minutes yellow tinge. Entered duodenum at 10:00. Tube removed, 11:00. Total quantity, 80 c.c., light yellow; alkaline; microscopic cell debris; red blood cells. Bilirubin, + +; urobilin, 1,000; urobilinogen, 0. Total, 1,000. Urine: bilirubin, 0; urobilin, 0.

Case 3.—J. B. Dec. 18, 1914. Diagnosis: ulcus ventriculi. Blood: count, etc., normal. Duodenal tube introduced, 9:10; opalescent; later light yellow; Congo, +; total acidity, 39; total free, 29; free nuclei; sporing yeast. Entered duodenum, 9:35. Tube removed at 10:20. Total, 50 c.c.; light yellow; opaque. Bilirubin, + +; urobilin, 100; urobilinogen, 0. Total, 100.

Case 4.—S. H., Dec. 26, 1914. Diagnosis: pernicious anemia. Blood: count, 1,500,000; hemoglobin, 30; index, 1; macrocytes and macroblasts; leukocytes, 3,500. Duodenal tube introduced, 9:30. Opalescent; later yellow; Congo negative. Entered duodenum, 10:10. Tube removed, 12:15. Total quantity, 60 c.c. Very dark chocolate yellow; alkaline. Bilirubin, + + +; urobilin, 2,000; urobilinogen, 1,800. Total, 3,800.[5]

Case 5.—M. M. Dec. 26, 1914. Diagnosis: gallbladder carcinoma.[6] Blood: normal. Duodenal tube introduced, 10:00. Much debris; Congo positive; total acidity, 60; free acid, 40; total quantity, 60 c.c.; microscopic, no sarcinae or yeast. Entered duodenum, 10:50; alkaline to litmus; milky; at no time yellow; total quantity, 35 c.c. Tube removed at 12:10. Bilirubin, 0; urobilin, 0; urobilinogen, 0. Total, 0.

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4. Postmortem eight months later revealed Laennec's cirrhosis with bleeding esophageal varices as the cause of the secondary anemia.

5. After keeping duodenal contents in open flask exposed to room light for eight hours, urobilin value was found to be 1,800 and urobilinogen 1,000. Hence, while urobilinogen was being converted into urobilin, the latter was also disappearing into an unknown form. After twenty-four hours all traces of both had disappeared.

6. Postmortem examination four months later revealed adenocarcinoma, primary, of gallbladder with complete obstruction of common duct by direct extension.

CASE 6.—J. F. J. Dec. 29, 1914. Diagnosis: secondary anemia. Blood: count, 2,500,000; hemoglobin, 17; index, 0.34; anisocytosis, poikilocytosis. Duodenal tube introduced, 10:00. Milky; much debris; Congo positive. Duodenum entered, 1:00; removed, 12:15. Quantity, 40 c.c.; light yellow. Bilirubin, + +; urobilin, 0; urobilinogen, 0. Total, 0.

CASE 7.—Mr. R. Jan. 5, 1915. Diagnosis: ulcus ventriculi. Blood: not recorded. Duodenal tube introduced, 9:35. Opalescent; after twenty-five minutes yellow tinge; quantity, 115 c.c.; Congo positive; total acidity, 60; free acid, 55; microscopic red blood cells; debris; no sarcinae. Entered duodenum, 10:00. Tube removed, 11:00. Quantity, 80 c.c.; light yellow. Opaque and stringy; alkaline at periods and again acid. Bilirubin, + +; urobilin, 600; urobilinogen, 600. Total, 1,200.

CASE 8.—A. R. Jan. 6, 1915. Laennec's cirrhosis. Blood: count, 4,700,000; hemoglobin, 85; index, 1—. Duodenal tube introduced, 9:00. Much mucus; later yellow tinge; Congo plus. Entered duodenum, 9:40. Tube removed, 10:40; quantity, 50 c.c.; faint yellow. Bilirubin, +; urobilin, 1,000; urobilinogen, 0. Total, 1,000. Urine: bilirubin, 0; urobilin, +.

CASE 9.—Miss M. Jan. 7, 1915. Vagotonia. Blood: negative. Duodenal tube introduced, 9:15; much salivation; opalescent; later yellow; Congo plus; total acid, 50; free acid, 45. Total gastric secretion, 70 c.c. Entered duodenum, 9:45. Yellow and opaque; alkaline and acid alternating; total, 30 c.c.; tube removed, 10:05. Bilirubin, + +; urobilin, 200; urobilinogen, 0. Total, 200. Stool: guaiac negative.

CASE 10.—J. S. Jan. 11, 1915. Diagnosis: gastric carcinoma. Blood: count, 1,900,000; hemoglobin, 37; index, 0.95; resistance, 0.45-0.25; normoblasts, megaloblasts. Duodenal tube introduced, 9:30. Milky; much debris; later yellow tinge; quantity, 55 c.c.; Congo, negative; Wolff-Junghans, positive, 1-400. Entered duodenum, 9:50. Tube removed, 10:50. Total quantity, 60 c.c.; very light yellow. Bilirubin, +; urobilin, 100; urobilinogen, 0. Total, 100. Stool: light color; guaiac positive repeatedly on meat free diet.

CASE 11.—Mr. E. Jan. 13, 1915. Diagnosis: hard liver. Blood: count, 4,500,000; hemoglobin, 70; leukocytes, 7,000; red cells chlorotic. Duodenal tube introduced, 9:00. Milky; much debris; later yellow; Congo negative; total, 50 c.c. Entered duodenum, 9:20. Light yellow; alkaline. Tube removed, 10:20; total, 30 c.c. Bilirubin, + +; urobilin, 100; urobilinogen, 0. Total, 100.

CASE 12.—Mrs. E. Jan. 15, 1915. Diagnosis: colloid goiter. Blood: not recorded. Duodenal tube introduced, 8:40. Milky; much mucus; Congo negative; total, 50 c.c. Microscopic, shreds of epithelium. Entered duodenum, 9:15. Removed, 10:00; total, 50 c.c.; light yellow. Bilirubin, + +; urobilin, 0; urobilinogen, 0. Total, 0.

CASE 13.—Mr. S. Jan. 19, 1915. Diagnosis: Laennec's cirrhosis. Blood: count, 5,500,000; hemoglobin, 98; index, 1—. Duodenal tube introduced, 9:00. Much debris; Congo negative; no Boas-Oppler bacilli. Entered duodenum, 9:35; removed, 10:00; total, 85 c.c.; medium yellow; much debris. Bilirubin, + +; urobilin, 1,200; urobilinogen, 0. Total, 1,200. Urine: bilirubin, 0; urobilin, +.

CASE 14.—J. C. Jan. 23, 1915. Diagnosis: cardiac incompensation; luetic. Blood: count, normal. Duodenal tube introduced at 9:20. Opalescent; later yellow; Congo positive; total acidity, 20. Entered duodenum, 9:45; normal yellow; alkaline; total in one hour, 50 c.c. Bilirubin + +; urobilin, 0; urobilinogen, 300. Total, 300. Urine: bilirubin, 0; urobilinogen, 600.

CASE 15.—J. H. Feb. 2, 1915. Diagnosis: pernicious anemia. Blood: count, 1,100,000; hemoglobin, 27; index, 1.2; normoblasts. Duodenal tube introduced, 9:40; first opalescent; much debris and shreds; later yellow tinged; Congo negative; total, 100 c.c.; no lactic. Entered duodenum, 10:20; very

dark chocolate yellow; alkaline; total, 30 c.c. Microscopically: bile casts. Bilirubin, + + +; urobilin, 4,000; urobilinogen, 2,800. Total, 6,800. Urine: bilirubin, 0; urobilin, 1,000.

Case 16.—Mr. H. Feb. 13, 1915. Diagnosis: pernicious anemia. Blood: count, 1,200,000; hemoglobin, 26; index, 1.2; normoblasts. Duodenal tube introduced, 9:15. Milky; much mucus; Congo negative. Entered duodenum, 10:00; removed, 10:50; total, 50 c.c.; very dark yellow; alkaline. Microscopically: negative. Bilirubin, + + +; urobilin, 2,000; urobilinogen, 1,200. Total, 3,200. Stool: very rich in urobilinogen. Urine: bilirubin, 0; urobilin, 1,000.

Feb. 25, 1915. Blood: count, 2,100,000; hemoglobin, 45; index, 1; no normoblasts. Duodenal tube introduced, 9:25; Congo negative, etc.; total, 35 c.c. Entered duodenum, 9:45; removed, 10:30; total, 40 c.c.; dark yellow. Bilirubin, + + +; urobilin, 1,200; urobilinogen, 1,000. Total, 2,200. Urine: urobilin +.

Table of Totals

No.	Disease	Bilirubin	Urobilin	Urobilinogen	Total
1	Pernicious anemia...	+ + +	+ + +	+ + +	+ + +
1	Pernicious anemia...	+ + +	3,000	3,000	6,000
1	Pernicious anemia...	+ + +	3,000	3,600	5,600
1	Pernicious anemia...	+ + +	1,600	2,000	3,600
1	Pernicious anemia...	+ + +	1,400	1,600	3,000
2	Secondary anemia...	+ +	1,000	0	1,000
3	Ulcus ventriculi....	+ +	100	0	100
4	Pernicious anemia...	+ + +	2,000	1,800	3,800
5	Gall bladder carcinoma	0	0	0	0
6	Secondary anemia...	+ +	0	0	0
7	Ulcus ventriculi....	+ +	600	600	1,200
8	Laennec's cirrhosis..	+	1,000	0	1,000
9	Vagotonia.....	+ +	200	0	200
10	Probable carcinoma	+	100	0	100
11	Liver path.....	+ +	100	0	100
12	Struma	+ +	0	0	0
13	Laennec's cirrhosis	+ +	1,200	0	1,200
14	Cardiac incompensation	+ +	0	300	300
15	Pernicious anemia...	+ + +	4,000	2,800	6,800
16	Pernicious anemia..	+ + +	2,000	1,200	3,200
..	Pernicious anemia..	+ + +	1,200	1,000	2,200
17	Mesarteritis syphilitica	+ +	0	0	0
18	Vagotonia	+ +	100	0	100
19	Pernicious anemia...	+ + +	2,300	2,500	4,800

Case 17.—Mr. Nic. C. March 9, 1915. Diagnosis: mesarteritis syphilitica. Blood: count, 6,000,000; hemoglobin, 83; chlorotic cells. Duodenal tube introduced, 9:20; opalescent; later yellow; Congo plus; total acidity, 36; free acid, 32; total, 50 c.c.; no yeast or sarcinae. Entered duodenum, 9:50; normal yellow; opaque; alkaline; total, 50 c.c. Bilirubin, + +; urobilin, 0; urobilinogen, 0. Total, 0.

Case 18.—P. A. March 17, 1915. Diagnosis: vagotonia. Blood: normal. Duodenal tube introduced, 9:30; watery; later yellow; total, 85 c.c.; total acidity, 102; free, 80; free nuclei. Duodenum entered, 10:30; opaque; yellow;

at times, only, alkaline; total, 60 c.c. Microscopic: negative. Bilirubin, + +; urobilin, 100; urobilinogen, 0. Total, 100.

Case 19.—Mr. W. April 13, 1915. Diagnosis: pernicious anemia. Blood: count, 1,300,000; hemoglobin, 30; index, 1.15; normoblasts and megaloblasts. Duodenal tube introduced, 9:00; opalescent; later yellow; little debris; Congo negative; total, 60 c.c. Entered duodenum, 9:15; dark chocolate yellow tint; removed, 9:45; total, 30 c.c. Bilirubin, + + +; urobilin, 2,300; urobilinogen, 2,500. Total, 4,800. Urine: urobilin, 1,000; urobilinogen, 100. Feces: very rich in urobilinogen; guaiac, 0.

SUMMARY

1. The early icteric feature of certain types of pernicious anemia is an expression of the primary fundamental hemolytic process of which the fully developed disease is a late bone-marrow exhaustion.

2. Eppinger's hypothesis of hypersplenie furnishes a pathologic basis for the increased hemolysis. Whatever the *causa causorum,* it must be regarded as established that it is through the instrumentality of the spleen that pathologic hemolysis is wrought.

3. The excessive hemolysis of pernicious anemia is attended by both a pleochromie and urobilinocholie.

4. Pleochromie is an expression of the immediate hemolysis; urobilinocholie of the heaped-up pigment in the portal system.

5. Whether in a crisis or remission period, pleochromie is a constant finding. This is in complete harmony with the fixed pathologic change in the spleen.

6. Urobilinocholie varies directly as the portal system is surcharged or becomes relatively empty of the plus of pigment. It is highest in crisis regardless of whether or not gross liver changes can be demonstrated.

7. Normally the duodenal secretion contains a certain level of bilirubin, occasionally urobilin, but never urobilinogen in considerable amounts.

8. In anemia of chronic gastro-intestinal hemorrhage in which the blood picture may simulate genuine pernicious anemia, the duodenal estimation of bile pigments will definitely yield an absence of pleochromie and urobilinocholie.

9. The most constant blood finding in genuine pernicious anemia is the high index. This is an expression of the overplus of hemoglobin-building material heaped up in the liver.

10. Essentially in both splenic anemia and in anemia of chronic gastro-intestinal hemorrhage, the process is one of abnormal blood loss; in the former the pigment moiety is saved to the organism; in the latter definitely and completely lost.

414 Syndicate Building.

BLOOD UREA DETERMINATIONS IN 211 CASES*

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LITERATURE REVIEW

Increased urea in the blood was first demonstrated in 1823 by Prevost and Dumas,[1] while working with nephrectomized animals. Bostock,[2] in 1829, noticed an increase in the blood urea of certain albuminurics. Richard Bright[3] with his co-workers—Prout, Babbington, and Christison (1836)—confirmed this observation and recognized it to be of clinical importance in nephritis. Babbington and Christison also made estimations of urea in body fluids.

Following the qualitative demonstration of blood urea, quantitative determinations were attempted by both French and German clinicians. Picard[4] (1856) was the first to determine that the amount of blood urea varies with the nitrogen intake.

Interest in the subject abated about this time, and for a period of forty years the references in the literature were infrequent. Schöndorff[5] (1899) revived the subject by an examination of the previous work, adding to it his own more accurate results, which confirmed the work of his predecessors. He observed that the urea fraction of the total nonprotein nitrogen of the blood was variable. Ascoli,[6] in 1901, using a precipitation method (acetic acid and sodium chlorid), and Strauss[7] (1902) with a similar method (heat and acetic acid), found that in cases of severe nephritis there was usually nitrogen accumulation. He found a marked increase in the terminal state. Müller[8] (1905) recognized urea retention to be of the highest value in diagnosing cases of uremia.

F. Widal and Javal[9] (1905) found that urea was retained in some cases of Bright's disease, and advocated a diminished protein diet in those cases.

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1. Prevost and Dumas: Ann. de chimie et de physique, 1823, xxiii, 90.
2. Bostock: Edinburg Med. and Surg. Jour., 1829, xxxii, 28.
3. Bright, Babbington, and Christison: Guy's Hosp. Rep., 1836, i, 360.
4. Picard: Thèse de Strassburg, 1856.
5. Schöndorff: Arch. f. d. ges. Physiol. (Pflüger's), 1899, lxxiv, 358.
6. Ascoli: Pfluger's Arch. f. path. Anat., 1901, lxxvii, 103.
7. Strauss: Die Chronische Niereutzündungen in ihrer Einwirkung auf die Blutflüssigkeit und deren Behandlung, Hirschwald, Berlin, 1902.
8. Müller: Verhandl. der deutsch. path. Gesellsch., 1904-5, vii-ix, Supplement 80.
9. Widal and Javal: Semaine méd., 1905, xxv, 313.

Von Noorden[10] (1907) obtained inconstant findings, but believed that the nitrogen accumulation in the blood constituted one of the most important phenomena of renal insufficiency.

Obermayer and Popper[11] (1909) confirmed the results of previous workers, finding the incoagulable nitrogen higher in uremic cases than in normal cases, and emphasized especially the increase in the urea fraction. They used heat and acetic acid for coagulation of blood proteins.

Hohlweg[12] (1911) used acetic acid and monopotassium phosphate, half saturated with sodium chlorid, to precipitate the blood proteins. He found increased values in uremia, but found them also in other conditions. While he considered nitrogen accumulation in the blood nonspecific of uremia, he thought it was of some prognostic value.

Widal[13] (1911) using the hypobromite method, based a prognosis on the amount of urea per liter; patients with 1 to 2 gm. per liter rarely live more than a year; with 2 to 3 gm. only months or weeks; and with more than 3 gm. a very short time. This prognosis, however, he did not apply to cases with renal obstruction, where such obstruction could be removed, as here he found the urea dropped when the obstruction was relieved. He found the retention was more permanent in chronic Bright's disease. He believed the amount of blood urea was of definite value in the prognosis, especially of those cases difficult to determine from the clinical symptoms alone.

Foster[14] (1912) using an alcohol precipitation and fractional separation method, found a considerable increase in nonprotein nitrogen in severe nephritis and in some other conditions. When the total nitrogen reached 1 gm. per liter, he regarded the prognosis as grave.

Rowntree and Fitz[15] (1913) used the original Widal method in part of their determinations, but in the main they precipitated by the Widal method and then determined the nitrogen by the Kjeldahl method. They reported the results obtained in fifty-seven cases. No increase of blood urea was found in suspected nephritis (i. e., clinically). In mild nephritis the average was 0.38 gm. urea per liter; in cases of advanced nephritis 0.783 gm. per liter; cases of cardiac decompensation without nephritis 0.70 gm. per liter; and cardiac decompensation associated with nephritis 0.831 gm. per liter. In summarizing, they believed that the accumulation of nonprotein nitrogen in the blood of nephritics was of considerable prognostic value. When

10. Von Noorden: Metabolism and Practical Medicine, 1907, ii, 486.
11. Obermayer and Popper: Ztschr. f. klin. Med., 1911, lxxii, 332.
12. Hohlweg: Deutsch. Arch. f. klin. Med., 1912, civ, 216.
13. Widal: Bull. et. mém. Soc. méd. d. hôp. de Paris, 1911, xxxii, 627.
14. Foster: The Archives Int. Med., 1912, x, 414.
15. Rowntree and Fitz: The Archives Int. Med., 1913, xi, 258.

it occurred it was confirmatory evidence of renal insufficiency, whereas the absence of such increase was of less importance. As a point in differentiating cardiac and renal diseases they believed it was also of importance.

Frothingham, Fitz, Folin and Denis[16] (1913) found that the blood urea and the phenolsulphonephthalein excretion varied from normal in animals subjected to experimental uranium nephritis, and the amount of such variation agreed with the amount of kidney destruction. They observed a gradual increase in urea as nephritis developed and a gradual decrease as the kidney recovered. They concluded that the urea in the blood is a measure of the difference between the waste nitrogen urea produced in metabolism and the amount excreted in the urine. Such a retention of nitrogen in experimental nephritis was found also by Siegel,[17] Pearce, Hill and Eisenbrey,[18] Austin and Eisenbrey,[19] Folin, Karsner, Howard and Denis[20] and Mosenthal[21] (uranium, cantharidin, chromate, etc., nephritis). Mosenthal stated that there "Seems no doubt that kidney insufficiency in these cases is responsible for the retention." Karsner[22] also found retention in experimental arsenical nephritis, especially during the stage in which tubular destruction was most marked.

Soper and Granat[23] (1914) studied a series of ninety-seven cases, observing the urea content in spinal fluids. Their work will be referred to later under discussion of body fluids.

Folin, Denis and Seymour[24] (1914) reported a series of clinical experiments showing the relation of the nonprotein nitrogen and of the urea of the blood of nephritics to the amount of protein intake. Under low protein diet they were able to reduce the urea content from 0.67 gm. per liter to practically a normal amount. They conclude that the rational means of determining protein tolerance is by determining the nonprotein nitrogen retention and not by blood pressure findings. They found no connection between nitrogen retention and blood pressure as had previously been described by Strauss, who believed that the high blood pressure of nephritics is frequently associated with nitrogen retention.

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16. Frothingham, Fitz, Folin, and Denis: THE ARCHIVES INT. MED., 1913, xii, 245.
17. Siegel: Ztschr. f. exper. Path. u. Therap., 1907, iv, 561.
18. Pearce, Hill, and Eisenbrey: Jour. Exper. Med., 1910, xii, 196.
19. Austin and Eisenbrey: Jour. Exper. Med., 1911, xiv, 366.
20. Folin, Karsner, Howard, and Denis: Jour. Exper. Med., 1912, xvi, 789.
21. Mosenthal: THE ARCHIVES INT. MED., 1914, xiv, 844.
22. Karsner and Denis: Jour. Exper. Med., 1914, xix, 63.
23. Soper and Granat: THE ARCHIVES INT. MED., 1914, xiii, 131.
24. Folin, Denis, and Seymour: THE ARCHIVES INT. MED., 1914, xiii, 224.

Agnew[25] (1914), using the method of Folin and Denis,[26] found in the majority of cases of nephritis, when the excretion of phenolsulphonephthalein was below 40 per cent., there was an increase in the nonprotein blood nitrogen and in the blood urea. This did not hold true in cases of cardiac decompensation. He found the incoagulable nitrogen determinations valuable in the diagnosis of incipient uremia, coma, and in conjunction with phenolsulphonephthalein in cardiorenal diseases.

Frothingham and Smillie[27] (1914), using the method of Folin and Denis, found many cases of chronic nephritis with normal nonprotein nitrogen in the blood. Cases showing 0.35 gm. per liter were clinically more severe than the cases with no retention, while the cases with 0.5 gm. or over were clinically of still more severe type. No nonnephritic cases showed nitrogen retention. They found that the excretion of phenolsulphonephthalein varied inversely with the retention of nitrogen, except in cases of cardiac decompensation. Blood pressure and pulse pressure they believed to be of less prognostic value than nitrogen retention.

Tileston and Comfort[28] (1914), following the technic of Folin and Denis, observed a large series of cases (142). Their most important deduction was that in chronic nephritis without uremia the urea values were normal or moderately elevated. Cases of uremia showed great increase without exception. The excretion of phenolsulphonephthalein was proportional to the nitrogen retention. Outside of uremia, extremely large urea values, over 1 gm. per liter, were encountered only in severe anemias and intestinal obstruction. They found retention in chronic plumbism, lobar pneumonia, syphilis (36 per cent. of cases), diabetes with coma, and acute yellow atrophy of the liver. Normal values were obtained in eclampsia, chronic passive congestion, compensated valvular lesions, pericarditis, endocarditis, acute rheumatism, uncomplicated scarlatina, cerebral hemorrhage, functional nerve diseases, diabetes without coma, myxedema, exophthalmic goiter, and malignant disease. They believed the estimation of nitrogen to be of the greatest value in the diagnosis of uremia and also in the prognosis of chronic nephritis. They thought that the total nitrogen was of more prognostic importance than the urea nitrogen.

Ovsiannikova[29] (1914) found a mortality of 18 per cent. in cases of chronic nephritis with blood urea below 0.5 gm. per liter; 18 per

25. Agnew: The Archives Int. Med., 1914, xiii, 485.
26. Folin and Denis: Jour. Biol. Chem., 1913, xiv, 29.
27. Frothingham and Smillie: The Archives Int. Med., 1914, xiv, 541.
28. Tileston and Comfort: The Archives Int. Med., 1914, xiv, 620.
29. Ovsiannikova: Russk. Vrach., 1914, xiii, 253.

cent. for 0.5 to 1 gm. per liter; 58 per cent. for 1 to 2 gm. per liter; and 85 per cent. for 2 to 5 gm. per liter.

Widal, Weill and Radot[30] (1914) found that the phenolsulphonephthalein test and the urea in the blood serum ran parallel. They rose and fell together in normal cases and in cases of Bright's disease. The mere estimation of the urea content of the blood from time to time they believed to be a reliable and accurate index of the azotemia. In chronic kidney disease when the urea was less than 0.5 gm. per liter there was no question of azotemia; when 1 gm., they believed the test should be frequently repeated; when 2 gm., the prognosis was bad.

TABLE 1.—Normal

Number	Age	Blood Pressure	Phthalein, Per Cent.	Blood Urea	
				Two Hours After Meals	Seventeen Hours Fasting
38	23	100	72	0.168	.....
39	21	102	87	0.168	0.120
40	21	122	67	0.156	0.156
41	21	122	82	0.120	.....
43	20	...	..	0.180	. ...
47	24	116	..	0.192	.....
58	22	100	67	0.192	.....
11	36	112	79	0.180	0.132
69	21	110	..	.....	0.108
77	23	...	65	0.160	.....
82	21	...	42	0.220	.....
83	23	126	60	0.216	.....
176	25	122	[illegible]	0.252	.....
195	20	120	50	0.204	.....
196	26	132	65	0.108	.....
197	22	120	70	0.120	.....

Farr and Krumbhaar[31] (1914) stated that in cirrhosis of the liver the total nitrogen was increased only in cases accompanied by definite nephritis. They did not support the view held by Morel and Mouriquand,[32] and by some other investigators, that in destructive diseases of the liver the percentage of urea to the total nitrogen was decreased; to the contrary, they found that the percentage of urea remained normal.

30. Widal, Weill, and Radot: Presse. méd., 1914, xxii, 565.
31. Farr and Krumbhaar: Jour. Am. Med. Assn., 1914, lxiii, 2214.
32. Morel and Mouriquand: Bull. et. mém. Soc. méd. d. hôp. de Paris, 1913, xxxv, 266.

Mosenthal[21] (1915), in a series of interesting experiments, was able to produce in dogs experimental uranium nephritis of two types. In nephritis of moderate severity there was an increase in nitrogen elimination. This increase he demonstrated experimentally to be due, not to any previous retention, but to an increased protein catabolism. The more severe cases showed a decreased elimination of nitrogen in the urine with a true nitrogen retention due to kidney insufficiency. He also showed that a gain or loss of water in the body was a factor that influenced the quantitative estimations of nonprotein nitrogen in the blood.

Foster[33] (1915) observed a series of cases of severe cardiac decompensation without nephritis, and found in them an increase in the nonprotein nitrogen averaging 0.6 gm. per liter. In four of these cases necropsy substantiated the clinical findings. The nonprotein nitrogen in chronic parenchymatous he found lower than in chronic interstitial nephritis. In general, he found the most pronounced nitrogen increase in cases with high arterial pressure. He states that uremia may occur when the nitrogen is low, that is, no higher than in a latent nephritis. The convulsive type of uremia showed a nitrogen content double that of the asthenic type. A high nonprotein nitrogen in the absence of uremic symptoms he believed to be of more definite prognostic value than in the presence of uremic symptoms, while a normal finding did not exclude a remotely fatal issue.

Rowntree, Marshall, and Baetjer[34] (1915) also reported two cases of myocardial insufficiency with necropsies showing no kidney change except chronic passive congestion. Clinically, both showed urea retention, 0.67 and 1.1 gm. per liter, respectively.

TECHNIC

We have used in this series of experiments the urease method of Marshall,[35] fully described by the author.

BLOOD UREA IN NORMAL CASES

The several observers have obtained widely varying values for the normal blood urea, largely due to the method employed. A glance at Table 2 will show this clearly.

Our observations cover a series of sixteen cases, all persons in apparently perfect physical condition. The urine in each case was normal. The average amount of blood urea obtained after seventeen hours fasting was 0.129 gm. per liter. Two and one-half hours after

33. Foster: The Archives Int. Med., 1915, xv, 356.
34. Rowntree, Marshall, and Baetjer: The Archives Int. Med., 1915, xv, 543.
35. Marshall: Jour. Biol. Chem., 1913, xiv, 283; ibid., 1913, xv, 487.

TABLE 2.—NORMALS OF VARIOUS AUTHORS

Gm. per Liter	Authors	Method
0.20 to 0.41	Foster	Alcoholic precipitation and fractional separation.
0.30 to 0.50	Rowntree and Fitz	Widal hypobromite and Kjeldahl.
0.61	Schöndorff (quoted by Agnew)	Phosphotungstic acid precipitation.
0.10 to 0.20	Strauss (quoted by Agnew)	Heat and acetic acid.
0.23 to 0.28	von Jaksch[37]	Phosphotungstic acid precipitation.
0.18	Obermayer and Popper	Heat and acetic acid.
0.31	Hohlweg	Dilute acid, 5 per cent. monopotassium phosphate and one-half saturated sodium chlorid.
0.11 to 0.14	Folin and Denis	Precipitation with methyl alcohol, then with zinc chlorid, hydrolized, Nesslerized, and colorimetry.
0.21	Aszacki[38]	Uranium acetate.
0.08 to 0.25	Farr and Austin[39]	
0.43	Farr and Austin (quoted by Hinman).	
0.30 to 0.50	Widal	Hypobromite method.
0.12 to 0.14 (2½ hours)	Tileston and Comfort	Technic of Folin and Denis.
0.13 to 0.20 (12 hours)	Tileston and Comfort	Technic of Folin and Denis.
0.05 to 0.07 (fasting)	Picard	Precipitation with alcohol and then Liebig's titration method.
0.11 to 0.13 (after food)	Picard	
0.50	Weill, Vallery and Radot[40] (quoted by Hinman)	

37. Von Jaksch: Leyden Festschr., 1902, i, 197.
38. Aszacki: Ztschr. f. klin. Med., 1913, lxxvii, 1.
39. Farr and Austin: Jour. Exper. Med., 1913, xviii, 228.
40. Widal, Weill, Vallery, and Radot: Jour. d'Urol., 1913, v, 68.

a heavy protein meal this was increased to 0.175 gm. per liter, or an average increase of 0.046 gm. per liter. Reference to Table 1 will show that the values obtained varied from 0.108 gm. per liter to 0.252 gm. per liter, in no case reaching 0.300 gm. per liter. The average per cent. of phenolsulphonephthalein excreted in two hours was 68.

RELATION OF PROTEIN INTAKE

That the amount of protein ingested had a distinct bearing on the quantity of blood urea, was observed by Picard in 1856. He found also that the time for taking blood for examination, with reference to food intake, caused certain variations. These observations have been repeatedly confirmed and emphasized by different authors.

Case 80, of our own observation, demonstrates this very clearly. A normal individual, with a phenolsulphonephthalein excretion of 60 per cent., had a blood urea of 0.326 gm. per liter. She gives a history of being a heavy meat eater. On a low protein diet for a period of three days the blood urea dropped to 0.168 gm. per liter; later, on a moderate protein diet the value increased to 0.240 gm. per liter. In nephritics, who have been given a low protein diet, we have also observed a drop in the blood urea (Case 56). The practical value of giving a low protein diet to decrease the nonprotein nitrogen in the blood of nephritics, has been recently demonstrated by various authors (Folin, Denis and Seymour, Tileston and Comfort, etc.).

CAUSES OF BLOOD UREA INCREASE

The finding of a normal as well as an increased amount of urea in nephritics, along with the fact that there is increased urea in numerous pathological conditions, in which no clinical or pathological evidence of nephritis exists, leads us to the conclusion that blood urea increase cannot be explained by renal insufficiency alone. Faulty kidney excretion, resulting in true nitrogen retention, is no doubt the chief factor in cases of nephritis, but many other cases cannot be explained on the basis of retention. We observe in some cases involving general metabolism, without any evidence of nephritis, an increased blood urea. Cases of exophthalmic goiter show a moderate increase. In one case we observed still greater increase during a condition of hyperthyroidism following a partial gland resection. This increase dropped to normal simultaneously with the improvement of the patient.

Whether increased protein catabolism alone explains these cases is difficult to state. There may be an abnormal urea combination in the blood, which makes elimination by the kidney impossible, as has been suggested by Mosenthal.

TABLE 3.—Acute Nephritis

No.	Age	Diagnosis	Kidney	Urine					Blood Pressure	Phthalein, per Cent.	Blood Urea	Remarks
				Quan., c.c.	Sp. Gr.	Alb.	Blood	Microscopic				
2	29	Puerperal septicemia	Acute toxic nephritis	Spec.	1.012	S. A.	Pos.	Many gran. casts	..	..	0.924	Death next day.
6	48	Lobar pneumonia	Acute toxic nephritis	Spec.	1.022	M. A.	Pos.	Blood casts	137	65	0.120	Recovery.
12	55	Acute bowel obstruction	Acute toxic nephritis	Spec.	.....	L. A.	Pos.	Many hy., gran. and blood casts	...	..	1.380	Died two days later.
34	54	Lobar pneumonia	Acute toxic nephritis	900	1.016	M. A.	Neg.	Gran. and hy. casts	118	..	0.480	Died one day later. Fourth day of disease.
36	44	Lobar pneumonia	Acute toxic nephritis	Spec.	1.016	S. A.	Pos.	Occ. gran. cast...	104	..	0.660	Fourth day of disease.
42	24	Lobar pneumonia	Acute toxic nephritis	Spec.	1.030	S. A.	Neg.	Hy. and gran. casts	...	..	0.264	Third day.
											0.288	Fifth day.
52	21	Lobar pneumonia	Acute toxic nephritis	Spec.	1.022	T.	Neg.	Occ. gran. cast; Occ. W.B.C.	...	..	0.396	Fifth day. Died next day.
54	34	Lobar pneumonia	Acute toxic nephritis	Spec.	1.022	M. A.	Neg.	Many hy. casts..	108	37	0.540	Second day. Recov.
60	22	Pregnancy (5 mo.)	Acute toxic nephritis	600	1.012	M. A.	Neg.	Few W.B.C.	126	40	0.180	3/10.
		Appendicitis.....		1,800	1.007	S. A.	Neg.	Many W. B. C.; Occ. hy. cast	...	..	0.264	3/20. Recovery.
71	55	Lobar pneumonia	Acute toxic nephritis	Spec.	1.018	T.	Neg.	Few gran. casts..	99	22	0.624	Died same day.
73	39	Lobar pneumonia	Acute toxic nephritis	Spec.	1.022	T.	Neg.	Few gran. and hy. casts; few W.B.C.	110	37	0.420	Second day after onset.
87	43	Lobar pneumonia	Acute toxic nephritis	Spec.	1.022	T.	Neg.	Occ. W.B.C.	94	42	0.384	Fourth day after onset.
95	27	Acute parenchymatous	.....	Spec.	1.022	M. A.	....	Many gran. and hy. casts; Occ. W.B.C.	120	37	0.360	
106	28	Lobar pneumonia	Acute toxic nephritis	.....	.....	.....	....	.....	90	55	0.300	Sixth day.
115	8	Primary anemia...	Acute toxic nephritis	Spec.	1.007	M. A.	Pos.	Few hy. casts; R.B.C.	92	..	0.597	Died two days later.
121	32	Acute pulmonary tuberculosis	Acute toxic nephritis	Spec.	1.022	L. A.	....	Hy. casts; few W.B.C.	110	T	0.600	Died next day.
122	43	Lobar pneumonia..	Acute toxic nephritis	Spec.	1.020	S. A.	Neg.	Occ. hy. and gran. casts; Occ. W.B.C.	112	62	0.456	Ninth day.
144	39	Common duct obstruction	Acute toxic nephritis	Spec.	1.018	T.	....	Many hy. and gran. casts	125	13	1.512	5/10. Bile in urine.
											1.560	5/11.
				900	1.014	T.	Pos.	Occ. hy. cast.....	...	20	0.936	5/14.
				250	1.023	T.	....	Occ. hy. cast.....	...	56	0.168	5/29. Sugar trace.
								Occ. W.B.C.	...	..	0.144	6/2.
151	37	Lobar pneumonia	Acute toxic nephritis	Spec.	1.023	M. A.	Neg.	Num. hy. casts...	140	38	0.660	Fourth day. Died same day.
156	32	Acute parenchymatous	.....	Spec.	1.015	M. A.	Pos.	Few hy. casts; W.B.C. and R.B.C.	134	26	0.720	5/15.
				1,000	1.008	M. A.	Pos.	Gran. and hy. casts	...	..	0.912	5/19.
										38	0.576	5/22.
				Spec.	1.008	T.	Pos.	Hy. and gran. casts; W.B.C.	130	50	0.672	5/25.
				Spec.	1.018	T.	Pos.	Hy. and cellular casts; R.B.C. and W.B.C.	...	75	0.336	5/31. Left hospital in fair condition.
163	30	Lobar pneumonia	Acute toxic nephritis	Spec.	1.017	S. A.	Neg.	Occ. hy. cast; Num. W.B.C.	112	64	0.444	Third day. Died same day.
175	25	Lobar pneumonia	Acute toxic nephritis	Spec.	1.025	T.	Pos.	W.B.C. and R.B.C	100	80	0.336	Second day.
178	39	Lobar pneumonia	Acute toxic nephritis	Spec.	1.018	T.	Neg.	Hy. and gran. casts; W.B.C.	...	68	0.552	Fourth day. Died next day.
181	42	Lobar pneumonia	Acute toxic nephritis	Spec.	.....	T.	Neg.	Occ. hy. cast; Occ. W.B.C.	140	70	0.636	Fourth day.
187	50	Meningitis.....	Acute toxic nephritis	Spec.	1.016	M. A.	Pos.	Occ. W. B. C.; many gran. casts	...	T	0.384	Fourth day. Died six hours later.

Cases of acute infection often present the same picture. Here there is undoubtedly increased catabolism along with the elevation of temperature. It seems quite probable that an abnormal urea compound, as well as an absolute increase in the amount of urea nitrogen formed, combined with kidney insufficiency of varying degree, occurs in the terminal state.

That pure circulatory disturbance may give rise to increase in blood urea has been demonstrated in cases of cardiac decompensation, where necropsy showed the absence of kidney lesions (Foster).

Another factor which has to be considered is the percentage of water in the body fluids. In cases of persistent vomiting, esophageal stenosis, acute hemorrhage, etc., we have observed an increase in the blood urea, and conversely, in a case of high blood urea, we have observed a distinct drop following the addition of a considerable quantity of water to the body fluids. Concentration of and dilution of the blood probably account in part at least for these phenomena.

UREA IN PATHOLOGICAL CONDITIONS

In studying various pathological conditions we have considered a blood urea above 0.250 gm. per liter as abnormal. For purposes of classification we have divided the cases into clinical groups, including (1) acute nephritis, (2) suspected chronic nephritis, (3) mild chronic nephritis, (4) advanced chronic nephritis, (5) advanced chronic nephritis with cardiac decompensation, (6) miscellaneous genito-urinary, (7) diseases of heart, (8) anemias, (9) acute infections, (10) chronic infections, (11) diabetes mellitus, (12) diseases of thyroid, (13) malignancy, (14) miscellaneous cases.

ACUTE NEPHRITIS

Twenty-five cases of acute nephritis were observed. Of these eighteen were toxic nephritis accompanying lobar pneumonia. The urea averaged 0.578 gm. per liter, thus showing a definite increase. Only three cases showed a normal amount of urea. All showed albumin and casts in the urine. Twenty-two phthalein tests were made; sixteen showed decreased elimination.

Case 12 of intestinal obstruction following operation showed normal urea before operation. With developing obstruction, many hyaline and granular casts, with a large amount of albumin, appeared in the urine. The blood urea was 1.390 gm. two days before death.

Cases 95 and 156 were acute parenchymatous nephritis of no determined etiology. Case 156 entered the hospital the third day of illness, complaining of weakness and headache. His previous history was entirely negative. He showed a medium amount of albumin, casts,

TABLE 4.—Suspected Chronic Nephritis

No.	Age	Diagnosis	Kidney	Urine					Blood Pressure	Phthalein, per Cent.	Blood Urea	Remarks
				Quan., c.c.	Sp. Gr.	Alb.	Blood	Microscopic				
3	50	Arteriosclerosis....	Arteriosclerotic	Spec.	1.020	T.	....	Occ. hy. cast.....	250	..	0.096	Hyperthyroidism.
				Spec.	1.026	T.	....	Occ. hy. cast.....	...	..	0.118	
7	72	Cystitis.....	Chronic interstitial nephritis	Spec.	1.005	T.	Pos.	Many W.B.C. Occ. gran. cast ..	150	..	0.084	
8	54	Headache.....	Chronic interstitial nephritis	Spec.	1.008	T.	....	Occ. hy. cast.....	135	..	0.210	
46	55	Prostatic hypertrophy	Chronic interstitial nephritis	Spec.	1.004	S. T.	....	....	190	..	0.288	
50	67	Suspected chronic nephritis	.....	1,500	1.012	S. T.	....	Occ. W.B.C.	122	77	0.288	
101	55	Suspected chronic nephritis	.....	1,800	1.015	S. T.	....	Occ. W.B.C. ..	120	65	0.264	
102	35	Edema.....	....	Spec.	.....	S. T.	....	Occ. hy. cast.....	130	..	0.336	
105	47	Suspected nephrolithiasis	.....	Spec.	.....	S. A.	Pos.	Occ. gran. cast...	180	70	0.242	4/21. B. P. 145 after 1 day in bed. 5/18.
										65	0.546	
114	60	Arteriosclerosis....	. ...	400	1.015	S. T.	....	Occ. hy. cast; Occ. W.B.C.	160	80	0.324	
127	65	Prostatic hypertrophy Suspected chronic nephritis	....	Spec.	1.023	S. T.	....	Many W.B.C.	134	72	0.240	
132	46	Suspected chronic nephritis	....	760	1.009	T.	....	Occ. W.B.C.	140	66	0.182	Dyspnea. Edema.
174	67	Hemorrhage, retina	....	Spec.	1.016	S. T.	Pos.	Occ. W.B.C.; Occ. R.B.C.; Occ. hy. cast	186	..	0.264	

white and red blood cells, a phthalein of 26 per cent., and urea of 0.720 gm. per liter. A few days later the urea rose to 0.912 gm. per liter. With improvement in symptoms the urea fell promptly and phthalein elimination increased to normal.

Case 144 was common duct obstruction. When the patient entered the hospital she showed blood urea of 1.512 gm. per liter, with 13 per cent. phthalein excretion. The common duct opened spontaneously and at the same time the accompanying nephritis began to clear. The urea and phthalein promptly returned to normal.

These cases followed practically the same course observed by the various investigators of acute experimental nephritis.

SUSPECTED CHRONIC NEPHRITIS

Twelve cases which were clinically suspected of being nephritis, showed an average urea of 0.248 gm. per liter, which is a normal value. The phthalein excretion was normal on all the cases which were examined. Reference to Table 4 will show the details of each case.

MILD CHRONIC NEPHRITIS

Table 5 shows the results in the nineteen cases of mild chronic nephritis. Of these five were parenchymatous and fourteen were interstitial nephritis. The average blood urea was 0.288 gm. per liter. Five of the cases showed normal blood urea. The phthalein excretion in this group was, with one exception, normal.

ADVANCED CHRONIC NEPHRITIS

Sixteen cases of advanced chronic nephritis came under our observation. The average blood urea of these cases was 0.444 gm. per liter. Three cases showed normal values.

Two cases of albuminuric retinitis associated with chronic parenchymatous nephritis were observed. It is interesting to note that both of these cases showed a normal urea. Widal has stated that albuminuric retinitis is always associated with azotemia. Tileston and Comfort had one case which also showed a normal urea value, but in the cases of long standing eye symptoms the urea was increased. Both of the cases coming under our observation were of brief duration, as far as the retinitis was concerned. It is of interest to note that in one case with a urea of 0.180 gm. per liter the excretion of phthalein was but 15 per cent.

One case of uremia was observed. This was of transitory character, following a prostatectomy. The maximum urea at the time the patient had uremic symptoms was 1.008 gm. per liter, with but a trace of phthalein excreted. This case is also of interest, because

TABLE 5.—Mild Chronic Nephritis

No.	Age	Diagnosis	Kidney	Urine					Blood Pressure	Phthalein, per Cent.	Blood Urea	Remarks
				Quan., c.c.	Sp. Gr.	Alb.	Blood	Microscopic				
49	53	.....	Chronic parenchymatous nephritis	1,400	1.016	T.	....	Occ. hy. cast; W.B.C.	178	..	0.242	
20	57	Diabetes mellitus..	Chronic interstitial nephritis	Spec.	1.030	T.	....	Occ. hy. cast.....	154	..	0.150	2 per cent. sugar.
				Spec.	1.012	T.	....	Occ. hy. cast.....	...	..	.....	No sugar on 60 gm. white bread per day.
10	54	Cystitis.....	Chronic interstitial nephritis	Spec.	1.008	T.	....	Occ. hy. cast.....	154	70	0.276	
44	56	Prostatic hypertrophy	Chronic interstitial nephritis	1,300	1.008	T.	....	Occ. hy. cast.....	180	75	0.168	
64	24	Post nephrectomy	Chronic interstitial nephritis	Spec.	1.005	S. T.	....	Occ. W.B.C.	128	50	0.264	
75	80	Prostatic hypertrophy	Chronic interstitial nephritis	Spec.	1.012	M. A.	Pos.	Many W.B.C.	137	T	0.393	Cystitis.
123	45	Chronic pulmonary tuberculosis	Chronic parenchymatous nephritis	Spec.	1.026	T.	....	Occ, hy. cast; W.B.C.	100	87	0.288	
135	40	Syphilis.....	.....	Spec.	1.020	T.	Pos.	R.B.C. and W.B.C.	118	..	0.312	Iritis.
138	35	Syphilis.....	Chronic interstitial nephritis	Spec.	1.011	S. T.	....	Few hy. casts....	112	..	0.242	
136	33	Syphilis.....	Chronic parenchymatous nephritis	Spec.	1.017	T.	....	Num. hy. casts...	162	77	0.480	
171	54	Syphilis.....	Chronic interstitial nephritis	Spec.	1.015	T.	....	Occ. hy. cast.....	170	..	0.420	
149	50	Tabes dorsalis.....	Chronic interstitial nephritis	Spec.	1.010	T.	....	Num. hy. casts...	140	..	0.312	
153	54	Arteriosclerosis....	Chronic interstitial nephritis	Spec.	1.006	S. T.	....	Occ. W.B.C.	190	..	0.264	Menopause.
180	34	Secondary anemia	Chronic interstitial nephritis	2,500	1.004	S. A.	....	Occ. hy. cast; W.B.C. and R.B.C.	140	62	0.264	
182	60	Chronic pulmonary tuberculosis	.....	Spec.	1.022	T.	....	Occ. hy. cast.....	96	80	0.372	
183	42	Chronic interstitial nephritis	.....	Spec.	1.008	S. T.	....	Occ. hy. cast.....	138	67	0.204	
192	25	Chronic pulmonary tuberculosis	.....	200	1.016	T.	....	Occ. hy. cast; few W.B.C.	...	..	0.120	
202	54	Diabetes mellitus..	Chronic interstitial nephritis	2,320	1.030	T.	....	Occ. hy. and gran. casts	242	65	0.300	5 per cent. sugar.
186	40	Chronic antrum infection	Chronic parenchymatous nephritis	Spec.	1.020	S. A.	....	Occ. hy. cast; Occ. W.B.C.	...	..	0.312	

TABLE 6.—Advanced Chronic Nephritis

No.	Age	Diagnosis	Kidney	Urine					Blood Pressure	Phthalein, per Cent.	Blood Urea	Remarks
				Quan., c.c.	Sp. Gr.	Alb.	Blood	Microscopic				
4	78	Prostatic hypertrophy	Chronic interstitial nephritis	1,400	1.015	S. T.	....	Occ. W.B.C. Occ. hy. cast	...	..	1.008	2/8.
5	26	Abortion. Albuminuric retinitis	Chronic parenchymatous nephritis	Spec.	1.016	L. A.	Pos.	Many hy. casts...	220	..	0.156	1/24. Before abortion.
				Spec.	1.010	L. A.	Pos.	Many hy. casts...	190	..	0.180	1/26. Post abortion.
				Spec.	1.010	L. A.	Pos.	Many hy. casts...	190	15	0.180	1/28.
											0.144	1 31.
				Spec.	1.016	M. A.	Neg.	Hy. and gran. casts	250	..	0.240	2/22. Retinitis still marked.
15	27	Albuminuric retinitis	Chronic parenchymatous nephritis	Spec.	.....	L. A.	Pos.	Many hy., gran. and blood casts	220	..	0.228	
16	33	Chronic parenchymatous nephritis	.....	Spec.	1.005	S. A.	Pos.	Hy. casts	...	..	.....	12/30.
				Spec.	1.008	T.	Pos.	Hy. and gran. casts	154	..	0.324	1/7. Patient in fair condition.
18	55	Chronic interstitial nephritis	....	Spec.	1.002	T.	Neg.	Occ. hy. cast; Occ. W.B.C.	230	..	0.276	
22	16	Chronic parenchymatous nephritis	.....	Spec.	1.015	L. A.	Pos.	Many casts	...	..	.....	1/8.
											0.319	3/2.
				Spec.	1.003	M. A.	Pos.	Occ. hy. and gran. cast	150	30	0.372	4 months' duration. 2/9.
28	33	Chronic interstitial nephritis	.....	2,800	1.006	T.	Neg.	Occ. hy. cast; Occ. W.B.C.	134	55	0.408	History of scarlet fever and syphilis. Mercurial treatment.
				5,500	1.010	S. T.	....	Occ. cast	...	..	.....	Limited fluids to 1,500 c.c. and gave 20 gm. NaCl in 24 hours.
48	51	Diabetes mellitus..	Chronic interstitial nephritis	480	1.025	T.	....	Occ. hy. cast; Occ. W.B.C.	168	55	0.144	2/28. Diabetes four years' duration. 2.5 per cent. sugar.
				750	1.015	T.	....	Occ. hy. cast.....	...	..	.....	3/1. 0.5 per cent. sugar.
51	51	Chronic parenchymatous nephritis	.....	1,200	1.012	M. A.	Pos.	Occ. hy. cast.....	...	47	0.480	3/5. Suspected nephrolithiasis.
											0.210	3 14.
56	63	Chronic interstitial nephritis	....	Spec.	1.016	M. A.	Neg.	Occ. hy. and gran. cast; Occ.W.B.C.	240	..	0.414	3/7.
				Spec.	1.015	M. A.	Neg.	Occ. hy. and gran. cast; Occ.W.B.C.	180	34	0.384	3/13. Six days' rest in bed.
76	29	Chronic parenchymatous nephritis	.. ..	Spec.	1.014	L. A.	....	Many hy. and gran. casts	250	50	0.396	Has mild edema, cardiac hypertrophy and pyorrhea
118	52	Chronic interstitial nephritis	.....	Spec.	1.013	T.	Neg.	Occ. hy. cast.....	170	..	0.276	Cardiac hypertrophy, mild edema, anemia, hematuria three years ago.
134	47	Chronic interstitial nephritis	.....	Spec.	1.010	L. A.	Pos.	Occ. gran. cast; R.B.C. and W.B.C.	163	..	1.080	Edema, ascites, dyspnea. One year's duration. Obesity.
172	58	Diabetes mellitus..	Chronic interstitial nephritis	2,200	1.033	M. A.	....	Occ. hy. cast; Occ. W.B.C.	...	..	0.362	Gangrene. 1.3 per cent. sugar. Diacetic and acetone.
					1.015	M. A.	....	Occ. hy. cast.....	...	..	.....	Sugar-free on carbohydrate-free diet.
184	42	Diabetes mellitus..	Chronic interstitial nephritis	Spec.	1.033	M. A.	....	Few W.B.C.; Occ. hy. cast	150	75	0.336	6/1. 5 per cent. sugar. Acetone and diacetic.
											2.340	6/6. Coma. Died next day.
191	58	.....	Arteriosclerotic	.. ...	1.025	T.	....	Many hy. casts; gran. casts	204	..	0.396	1/12.

TABLE 7.—Advanced Chronic Nephritis with Cardiac Decompensation

No.	Age	Diagnosis	Kidney	Urine					Blood Pressure	Phthalein, per Cent.	Blood Urea	Remarks
				Quan., c.c.	Sp. Gr.	Alb.	Blood	Microscopic				
1	75	Bronchitis. Myocarditis	Arteriosclerotic	400	1.022	M. A.	Pos.	Occ. hy. cast.....	...	..	0.518	1/14.
				800	1.018	T.	....	Few gran. casts; few W.B.C.	190	15	0.694	1/20. Died 1 23/15.
139	62	Myocarditis. Alcoholic cirrhosis	Chronic parenchymatous nephritis	200	1.019	S. A.	Pos.	R. B. C. and W.B.C.; hy. and gran. casts	135	T	0.438	5/8. Cyanosis. Dyspnea.
				Spec.	1.023	M. A.	....	W.B.C. and hy. casts	...	..	0.768	5/12. Delirium. B. P. 190 two years ago. Death 5/20/15.
141	54	Syphilis.....	Chronic interstitial nephritis	Spec.	1.015	S. T.	....	Occ. hy. cast.....	170	..	0.420 0.768	
143	69	Arteriosclerosis. Myocarditis	Arteriosclerotic	Spec.	1.015	S. A.	....	Hy. and gran. casts; W.B.C.	220	..	0.480	Pulsus alternans.
152	62	Myocarditis.....	Chronic interstitial nephritis	Spec.	1.030	S. A.	....	Occ. hy. cast.....	185	T	0.285	Dyspnea. Auricular fibrillation. Large liver.
161	56	Arteriosclerosis. Myocarditis	Arteriosclerotic	Spec.	1.014	T.	....	Few hy. casts; Occ. W.B.C.	242	.	0.336	Edema. Dyspnea.

TABLE 8.—Miscellaneous Genito-Urinary Cases

No.	Age	Diagnosis	Kidney	Urine					Blood Pressure	Phthalein, per Cent.	Blood Urea	Remarks
				Quan., c.c.	Sp. Gr.	Alb.	Blood	Microscopic				
4	78	Prostatic hypertrophy. Cystitis. Acute retention	Chronic interstitial nephritis	Spec.	1.004	S. A.	Pos.	Few W.B.C.	190	20	0.194	1/20. Before operation.
											0.306	1/21.
									190	20	0.864	One day before operation.
											0.960	1/30. Three days after operation.
											0.768	2/4. Hiccough, drowsiness.
											0.954	2/7. Symptoms of uremia.
											1.008	2/8.
											0.864	2/11.
											0.714	2/19.
											0.360	2/26.
											0.354	3/10.
										9	0.108	4/12.
											0.108	4/13. Patient went home.
10	54	Cystitis.....	Chronic interstitial nephritis	Spec.	1.008	T.	Neg.	Occ. hy. cast; Occ. W.B.C.	154	70	0.276	1/30. Old nephritic abscess calcified; drained 1 month previously.
29	28	Pyelonephritis.....	Large right kidney..	500	1.014	T.	Neg.	Few W.B.C.	120	70	0.336	Before operation.
44	54	Prostatic hypertrophy	Chronic interstitial nephritis	1,300	1.008	T.	Neg.	Occ. hy. cast.....	180	75	0.168	Two days before operation
45	56	Hydrocele.....	Negative	Spec.	1.020	T.	Neg.	Occ. hy. cast.....	..	67	0.340	
51	54	Suspected nephrolithiasis	Chronic parenchymatous nephritis	1,200	1.012	M. A.	Pos.	Few W.B.C.	..	47	0.480	3/5/10
								Few R.B.C.; Occ. hy. cast	...	.	0.240	3/11.
64	24	Post nephrectomy	Mild chronic nephritis	500	1.005	S. T.	....	Occ. W.B.C.	128	50	0.264	Nephrectomy four months previously; one-half of horseshoe kidney removed.
68	50	Pyonephrosis.....	.....	200	1.018	T.	Pos.	Occ. W.B.C.	126	54	0.360	3/18.
										24	0.516	3/30. Two days post nephrectomy.
									140	.	0.300	4/10.
				Spec.	1.016	T.	....	Occ. W.B.C.	...	30	0.264	5/1.
75	80	Prostatic hypertrophy	Mild chronic nephritis	Spec.	1.012	M. A.	Pos.	Many W.B.C.	137	..	0.264	3/23.
											0.264	4/7. Operation 3/31.
											0.284	4/26.
											0.293	
97	53	Nephrolithiasis....	.....	500	1.022	S. T.	. ..	Many W.B.C. . ..	120	25	0.444	4/13.
											0.444	4/23. One day after thyroidectomy.
									98	..	0.336	4/26. Five days after thyroidectomy. Marked tetany.
99	34	Pyelitis.....	... .	500	1.020	S. A.	Pos.	Many W. B. C.; many R.B.C.	115	57	0.312	
108	47	Polycystic kidneys	.....	2,200	1.015	M. A.	....	Occ. hy. cast; few W.B.C.	152	T	2.960	4/23. Urea taken. 6/27. Patient still living.

TABLE 9.—Diseases of the Heart

No.	Age	Diagnosis	Kidney	Blood Pressure	Phthalein, Per Cent.	Blood Urea	Remarks
26	22	Double mitral	Negative	130	..	0.252	Old history of rheumatism. Compensation good.
33	17	Double mitral	Negative	100	75	0.324	Severe tonsillitis and arthritis. Compensation good.
63	60	Double mitral	Negative	167	72	0.180	Mild decompensation.
109	47	Myocarditis. Pleurisy. Relative mitral insufficiency	Negative	142	82	0.180	Mild decompensation.
158	56	Myocarditis (mild)	Negative	120	..	0.276	Dyspnea. Chronic cough. Edema of feet. Mild decompensation.
165	64	Myocarditis	Negative	162	68	0.168	Marked edema of feet. Mild decompensation.
188	45	Myocarditis	Negative	130	..	0.180	Cardiac asthma.
193	45	Myocarditis	Negative	103	70	0.300	Dyspnea.
197	45	Myocarditis	Negative	102	..	0.336	Wassermann two plus. Dyspnea.
201	45	Double mitral	Negative	120	..	0.204	
203	68	Myocarditis	Negative	168	..	0.380	Heart markedly dilated. Gastric distress.

TABLE 10.—Anemias

No.	Age	Diagnosis	Kidney	R. B. C. Per c.mm.	Hem. Per Cent.	W. B. C. Per c.mm	Blood Pressure	Phthalein, Per Cent.	Blood Urea	Remarks
31	60	Primary anemia..	Negative	1,940,000	45	6,400	119	67	0.456	One year duration.
115	8	Primary anemia..	Parenchymatous nephritis	1,200,000	24	19,400	92	..	0.597	Six weeks' duration. Two days before death.
			Alb. Med. Amt.							
			Blood	660,000	12	18,200	...	..	1.778	Blood, heart ... (6 hours p. m.)
			Hy. casts						1.680	Pericardial fluid (6 hours p. m.)
132	14	Primary anemia..	Negative	550,000	14	3,000	110	..	0.255	Functional heart murmur. Anemia six months' duration.
37	36	Secondary anemia	Negative	2,240,000	40	16,100	80	..	0.168	Acute hemorrhage from puncture wound of back.
173	46	Secondary anemia	Negative	2,950,000	35	8,000	118	..	0.300	Acute hemorrhage from fibroid uterus. Two weeks' duration.
180	34	Secondary anemia	Chronic interstitial nephritis. Sp. Gr. 1.004 Alb. small amt. Occ. hy. cast	2,700,000	20	6,200	140	62	0.264	Fibroid uterus. Hemorrhage over period of four years.
185	38	Secondary anemia	Negative	2,730,000	35	6,000	150	..	0.168	Fibroid uterus. Hemorrhage over a period of three years.

of the progressive decrease of blood urea to normal, while the phthalein excretion remained small (9 per cent.).

That a high urea can occur without uremic symptoms is shown in Case 134. This case of chronic interstitial nephritis had a blood urea of 1.080 gm. per liter.

One case of diabetic coma with chronic interstitial nephritis had 2.340 gm. per liter, probably as a terminal condition.

The cases on which a phthalein test was made practically all show a distinct decrease along with the rise in blood urea.

ADVANCED CHRONIC NEPHRITIS WITH CARDIAC DECOMPENSATION

The average blood urea in this series of cases was 0.523 gm. per liter, which is higher than the same group of cases without cardiac decompensation, and also distinctly increased above normal value. The blood pressure of all these patients was distinctly elevated. The phthalein was just a trace in two cases, 15 per cent. in another case. Two of the cases with the highest blood urea (0.694 and 0.768 gm. per liter) died shortly after the test was made. Case 141 with a urea of 0.768 gm. per liter was in a fairly good physical condition at time of observation. No normal values were obtained in this group of cases.

MISCELLANEOUS GENITO-URINARY CASES

Twelve miscellaneous cases have been recorded under Table 8. Three cases of prostatic hypertrophy were observed, each having a definite nephritis. One case showed a normal value; the others were increased. Case 4 is interesting in that it shows a rise of blood urea from 0.194 to 0.864 gm. per liter associated with a partial urinary retention progressing to a complete retention. After operation the patient had typical uremic symptoms with a blood urea of 1.008 gm. per liter. As the patient improved the blood urea dropped progressively until a normal value was reached (0.108 gm. per liter). The patient was in fairly good condition at this time.

We found increased urea in cases of nephrolithiasis, pyelonephritis, and pyonephrosis, cystitis, and pyelitis. The cystitis was complicated with chronic interstitial nephritis.

We had under observation a very interesting case of polycystic kidneys (Case 108). Both kidneys were markedly enlarged, the excretion of phthalein was practically nil, and the patient was suffering from chronic uremia. The blood urea was 3.360 gm. per liter, which is the highest value we have obtained in any case. It is remarkable in that the patient is living, three months after the urea examination was made.

DISEASES OF THE HEART

Four cases of double mitral lesions were observed. Three showed normal blood urea. One case had a severe tonsillitis and arthritis and showed a slight increase in blood urea (0.324 gm. per liter). Four of the seven cases of myocarditis were slightly elevated. In no instance did the blood urea increase to 0.400 gm. per liter.

ANEMIAS

Rowntree and Fitz (1913) report a case of splenic anemia with polyserositis with a blood urea of 0.280 gm. per liter.

Tileston and Comfort (1914) obtained normal or only slightly raised blood ureas in two cases of secondary anemia due to hemorrhage and in one case of Banti's disease. In two cases of hemolytic anemia they found marked retention, 0.597 and 0.790 gm. per liter.

We have studied three cases of hemolytic anemia (primary) and four of secondary anemia due to hemorrhage. Two of the cases of secondary anemia had a normal blood urea; the other two cases showed only a mild increase. Two cases of chronic pernicious anemia showed 0.456 gm. and 0.255 gm. per liter, respectively. Case 115 was a very acute pernicious anemia in a child, terminating fatally in six weeks. Two days before death the blood urea was 0.597 gm. per liter; six hours postmortem the urea in heart's blood was 1.778 gm. per liter. He developed a terminal nephritis with many hyaline and blood casts.

LOBAR PNEUMONIA

Tileston and Comfort (1914) report blood ureas on fourteen cases of lobar pneumonia. The highest value was 0.360 gm. per liter, the lowest 0.112 gm. per liter. They believed there was no relation between retention and prognosis. Foster (1915) found a rise in non-protein nitrogen in lobar pneumonia exceptional and associated only with marked circulatory disturbance.

We made forty-two blood urea determinations on twenty cases of lobar pneumonia. These ranged from 0.120 gm. per liter to 1.044 gm. per liter, with an average of 0.405 gm. per liter. In thirty-six of the ureas the values were higher than normal; many of the cases showed a rather marked increase. Some of these patients were cyanosed at the time blood was taken but a number were not. Seventeen of the twenty cases ran a definite toxic nephritis, which probably helped to increase the blood urea. Only one case with a urea of over 0.6 gm. per liter recovered. We believe that in cases with marked increase a bad prognosis should be given. We found in cases of recovery the maximum increase was about the time of crisis, but most of our cases even on the first and second day after onset showed some urea retention. For more details the reader is referred to Table 11.

No.	Age	Day of Disease	Complications	Blood Pressure	Phthalein, Per Cent.	Blood Urea	Remarks
6	48	....	Toxic nephritis	137	65	0.120	Temperature 105 F. Recovered.
34	54	4th	Acute toxic nephritis	118	..	0.480	Temperature 104 F. Died next day.
36	44	4th	Acute toxic nephritis	104	..	0.660	Temperature 105 F. Died next day.
42	24	3d	Mild acute toxic nephritis	...	..	0.264	Temperature 104 F. Prompt recovery.
		5th	Mild acute toxic nephritis	...	..	0.288	Nephritis cleared up.
52	21	8th	Mild acute toxic nephritis	...	..	0.396	Temperature 105 F. Died one day later.
54	34	1st	Acute toxic nephritis plus syphilis	108	..	0.540	Temperature 105 F.
		5th		...	..	0.276	
		8th		...	37	0.540	Crisis ninth day.
		10th		...	..	0.220	
		14th		...	..	0.156	Recovery.
59	34	2d	Negative	92	67	0.156	Temperature 103 F. Recovery.
71	55	7th	Mild acute toxic nephritis	99	22	0.624	Temperature 105 F. Died one day later.
73	39	1st	Severe acute toxic nephritis	110	..	0.384	Temperature 103 F.
		2d		...	37	0.420	
		4th		...	..	0.372	
		6th		...	..	0.300	Afebrile.
87	43	4th	Mild acute toxic nephritis	94	..	0.384	Temperature 105 F.
		7th		115	..	0.228	
		12th		...	42	0.344	Afebrile.
		15th		...	..	0.480	Afebrile. Recovery.
106	28	4th	Mild acute toxic nephritis	88	55	0.180	Temperature 104 F.
		6th		...	..	0.300	
		9th		90	..	0.156	Recovery.
122	43	5th	Mild acute toxic nephritis	112	62	0.360	Temperature 103 F.
		9th		...	..	0.456	
		16th		..	..	0.408	Afebrile. Recovery.
		20th		...	..	0.300	Afebrile. Recovery.
151	37	2d	Severe acute toxic nephritis	110	38	0.360	Temperature 105 F.
		4th		140	..	0.660	Temperature 105 F. Died on fourth day
163	30	3d	Acute toxic nephritis	112	64	0.444	Temperature 105 F. Died one day later
164	29	5th	Negative	100	63	0.420	Temperature 104 F.
		7th		110	..	0.336	Recovery.
169	40	2d	Negative	108	78	0.336	Temperature 105 F.
		4th		...	..	0.516	Marked cyanosis.
		8th		...	..	1.044	Died on tenth day.
175	25	2d	Mild acute toxic nephritis	100	80	0.336	Temperature 105 F.
		6th		...	..	0.276	Recovery.
178	39	4th	Mild acute toxic nephritis	120	68	0.552	Temperature 104 F. Died next day.
181	42	4th	Mild acute toxic nephritis	140	70	0.636	Temperature 105 F.
		6th		...	..	0.456	
		9th		...	..	0.420	Recovery.
182	60	8th	Pulmonary tuberculosis	96	80	0.372	Temperature 103 F. Died from tuberculosis later.

TABLE 12.—Septicemia

No.	Age	Diagnosis	Kidney	Blood Pressure	Phthalein, Per Cent.	Blood Urea	Remarks
2	29	Puerperal septicemia (streptococcus)....	Acute toxic nephritis....	...	..	0.924	Death next day.
70	28	Streptococcus septicemia. Knee infection	Acute toxic nephritis....	...	24	0.432	3/19/15.
						0.516	3/20/15.
				110	..	0.348	3/24/15.
						0.240	3/30/15.
						0.308	4/ 1/15.
				102	..	0.180	4/ 8/15.
						0.120	4/10/15. Died two days later from acute hemorrhage due to perforation of vessel.
93	16	Streptococcus peritonitis. Infection from operation	Negative previous to operation	...	..	1.272	4/9/15. Died ten hours later, six days after operation.

TABLE 13.—Meningitis

No.	Age	Diagnosis	Kidney	Blood Pressure	Blood Urea	Urea Spinal Fluid	Remarks
110	51	Streptococcus meningitis from otitis media	Negative.....	68	0.708	.....	Patient died seven hours later. Mastoid operation day before.
126	35	Streptococcus meningitis from otitis media	Occult blood, otherwise negative	148	0.370	0.324	Died next day. Streptococcus found in spinal fluid.
130	53	Acute meningitis. ? Meningococcus.....	Negative.....	118	0.228	0.225	5/ 4 15. 1,500 cells per c.c. in spinal fluid.
						0.180	5/11/15. W. B. C., 20,000; phthalein 62%.
				142	.....	0.120	5/20/15. 39 cells per c.c.
187	50	Streptococcus meningitis.....	Acute parenchymatous nephritis	...	0.384	.....	10 a. m.
						0.798	4 p. m. Phthalein, trace only. Carbuncle. Pleurisy. Died at 5 p. m.

SEPTICEMIA

A single case of puerperal sepsis with recovery we find reported in the literature by Tileston and Comfort, with a normal blood urea.

Three cases of streptococcic septicemia came under our observation, all terminating fatally. Two of these patients developed severe acute toxic nephritis. The urine was not obtained from the third.

In Case 2 of puerperal septicemia the patient had a blood urea of 0.924 gm. per liter, and died within twenty-four hours; Case 93, general peritonitis, a patient with a blood urea of 1.272, died within ten hours; Case 70 had a blood urea of 0.516 gm. per liter on March 20, 1915, which dropped progressively to 0.120 gm. per liter on April 10, 1915, when the patient died from acute hemorrhage.

MENINGITIS

Three cases of streptococcic meningitis and one case of meningococcic meningitis were observed. The three cases of streptococcic meningitis showed definite increase in the urea; that of meningococcic meningitis showed normal urea (Table 13).

ROCKY MOUNTAIN SPOTTED FEVER

Only one case of spotted fever was observed. This was in a patient on the sixth day after onset, with marked petechial eruption, mild delirium and cyanosis. The blood showed 0.690 gm. of urea per liter. At the time there was only a trace of albumin in the urine. The patient died two days later.

TABLE 14.—ROCKY MOUNTAIN SPOTTED FEVER

No.	Age	Urine	Blood Urea	Remarks
154	17	Trace albumin	0.690	Died two days later.

SYPHILIS

Folin and Denis in 1913 reported sixty-three cases. Of these 46 per cent. showed a moderate elevation in blood urea.

Tileston and Comfort (1914) observed eleven cases. Approximately 50 per cent. showed increase of blood urea. They found albumin and casts in practically all of their cases, and concluded that the kidney was affected in a considerable percentage of syphilitics. Nitrogen retention was more evident in the tertiary stage, according to their observation.

Thirty-nine cases of demonstrable syphilis and four cases of clinically suspected syphilis are included in our series and the results are recorded in Table 15.

TABLE 15.—Syphilis

No.	Age	Kidney	Blood Pressure	Phthalein, Per Cent.	Blood Urea	Stage	Special Symptoms	Wassermann	Remarks
171	18	Negative	140	..	0.168	1	Primary on lip	++	No treatment.
206	34	Negative	132	..	0.360	1		—	Primary three days.
119	28	Negative	118	..	0.144	2		++	Six salvarsans and mercury.
124	24	Negative	155	..	0.264	2		++++	Three salvarsans and mercury.
129	33		130	..	0.360	2	Ulcer tongue	++++	No treatment. Two years' duration.
135	40	Mild parenchymatous nephritis	118	..	0.312	2	Iritis	++	Little treatment.
138	35	Mild chronic interstitial nephritis	112	..	0.242	Late 2		+	Infection ten years ago. Well treated then.
141	54	Chronic interstitial nephritis	170	..	0.420 0.768	Late 2	Pain	+	Primary twenty-one years ago. Little treatment.
142	35	Negative	105	..	0.288	Early 2	Adenitis	++	Three salvarsans and mercury.
145	30	Negative	120	..	0.366	2	Rectal syphilids	+++	No treatment.
146	28	Negative	118	..	0.276	2	None	+	Four salvarsans.
155	34	Negative	135	..	0.240	2	None	++	Primary eight years ago. Treatment three years.
166	22		144	..	0.225	2	Mucous patches, mouth and rectum	+++	Primary eight months ago. No treatment.
170	32	Negative	120	.	0.120	2	Maculopapular eruption	+++	No treatment.
179	28	Negative	...	..	0.350	2	No symptoms now	—	Five salvarsans and mercury for eight months.
21	41	Negative Negative	120 120	.. ..	0.222 0.168	3 3	Ulcer nasal septum	++++	No treatment. Four salvarsans and mercury for four months.
67	40	Negative	148	..	0.156	3	Ulcer of palate and perforation	+++	No treatment.
88	28	Negative	122	..	0.180	3	Perforation palate	++++	No treatment.
89	25	Negative	115	.	0.180	3	Pain in legs	+++	No treatment.
92	27	Negative	117	70	0.336	3	Hoarseness	+++	No treatment.
94	40	Negative	...	..	0.240	3	Iritis. Opaque vitreous	++++	Two salvarsans two months previously.
98	35	Negative	...	..	0.204	3	Acute anisocoria	+	
103	30	Negative	126	..	0.192	3	Six miscarriages	++++	No treatment.
104	35	Negative	142	..	0.204	3	Acute diplopia	+++	No treatment.

107	45	Negative...	102	45	0.336	3	Myocarditis.....	++	No treatment.
111	30	Negative.....	...	..	0.360	3	Diplopia.....	++	Little treatment four years ago.
113	26	Negative...	145	..	0.324	3	Gumma of clavicle.....	++++	No treatment.
136	33	Chronic parenchymatous nephritis	162	77	0.480	3	Laryngismus stridulus	++	Three salvarsans and mercury.
136	33	Chronic parenchymatous nephritis	...	.	0.360	.....	Laryngismus stridulus		
147	25	Negative.....	...	.	0.264	3	Iritis.....	++++	Three salvarsans and mercury.
157	45	Negative.....	142	.	0.348	3	Extra-ocular paralysis	++++	No treatment.
162	24	Negative..... ..	120	..	0.240	3	....	+ +	No treatment.
190	45	Negative.....	140	90	0.256	3	Facial paralysis	+	Four salvarsans and mercury.
199	42	Negative.....	172	..	0.180	3	Anisocoria. Fixed pupils.....	++++	Treatment sixteen years ago.
200	32	Negative.....	120	..	0.216	3	Girdle pain	++	Two salvarsans and mercury.
204	60	Negative.....	132	..	0.216	3	Leukoplakia.....	++++	Two salvarsans four years ago.
23	35	Negative.....	116	..	0.390	Paresis	Reflexes increased. Amnesia. Aphasia...	++	Six salvarsans.
125	49	Negative	...	.	0.204	Paresis	Hyper. K. K. Mental deterioration. Argyll Robertson pupils	++++	No treatment.
119	50	Chronic interstitial nephritis	140	..	0.312	Tabes	Absent K. K. Argyll Robertson pupils. Lightning pains	++++	No treatment.
198	41	Negative..	120	.	0.276	Tabes	Diplopia. Absent K. K. Argyll Robertson pupils. Adenitis (T.B.) Hem. 40%	++++	No treatment.

TABLE 16.- SUSPECTED SYPHILIS

No.	Age	Kidney	Blood Pressure	Phthalein, Per Cent.	Blood Urea	Spinal Fluid	Stage	Special Symptoms	Remarks
84	49	Negative.....	150	60	0.312	0.324	3	Cerebrospinal.....	Perforated septum. Arteriosclerosis. Wassermann negative.
79	57	Negative..... .	130	..	0.228	0.258	3	Cerebrospinal. Falling spells. Arcus senilis	Wassermann negative in blood and spinal fluid. Two cells per c.mm. spinal fluid.
66	45	Negative.. . ..	...	..	0.144	0.120	3	Vertigo. Gastric disturbances	Wassermann negative in blood and spinal fluid.
205	35	Negative..... ..	128	..	0.210	. ..	3	External strabismus. Diplopia	Wassermann negative.

Two cases were primary lues and one of these showed an increase in blood urea. Neither case showed any evidence of kidney pathology.

There were thirteen cases in the secondary stage. Eight showed an elevation of blood urea (i. e., above 0.250). Three of these had a distinct nephritis. Five cases showed an increase above 0.300 gm. per liter, four of whom had practically no treatment for their syphilis.

Twenty cases of the tertiary stage were studied. Eight of these showed an increased urea. But two cases had evidence of a distinct nephritis. Four of the five patients in whom the urea was over 0.300 gm. per liter had received no treatment.

Paresis and tabes dorsalis were each observed in two instances. The urea was elevated in one paretic and in both cases of tabes. One case of tabes had an interstitial nephritis.

SUMMARY

To summarize our observations:

1. Twenty of the thirty-nine cases showed an elevated blood urea (approximately 50 per cent.); of the primary stage 50 per cent., secondary 62 per cent., tertiary 40 per cent., and quarternary 75 per cent.

2. But six cases had evidence of a nephritis.

3. Nearly 80 per cent. of the thirteen cases in whom the blood urea was over 0.300 gm. per liter had received no treatment.

4. No relation between the Wassermann test and the amount of blood urea can be drawn.

5. The highest urea was 0.768, a patient who had acquired syphilis twenty years ago, and has now a chronic interstitial nephritis.

6. It is interesting to note that of the cases who received three or more salvarsans, but one was increased above 0.300 gm. per liter.

PULMONARY TUBERCULOSIS

A glance at Table 17 will show that in two cases out of seven, there was an increase in blood urea. Case 121, an acute miliary tuberculosis, with a severe acute toxic nephritis, had 0.600 gm. urea per liter, and terminated fatally. Case 123, a chronic advanced tuberculosis, was slightly raised (0.288 gm. per liter), and had a mild parenchymatous nephritis. Other authors have observed retention in cases of tuberculosis (Tileston and Comfort).

DIABETES MELLITUS

Seven cases of diabetes mellitus are included in our series (see Table 18). Five of these were complicated with chronic nephritis. Three of the cases showed definite increase in blood urea. They were all cases with nephritis. Case 184 had urea 0.336 gm. per liter on admission to the hospital. Two days later he developed coma and had a blood urea of 2.340 gm. per liter. He died the following day.

TABLE 17.—Pulmonary Tuberculosis

No.	Age	Stage of Disease	Kidney	Blood Pressure	Phthalein, Per Cent.	Blood Urea	Remarks
24	40	Mild chronic	Negative	120	45	0.150	Twenty years' duration.
121	32	Acute miliary	Acute toxic nephritis	110	T.	0.600	Temperature 103 F. Died.
123	45	Chronic advanced	Mild parenchymatous nephritis	100	87	0.288	
168	50	Chronic advanced	Negative	104	..	0.132	Temperature 100 F. Syphilis complicating.
192	25	Chronic advanced	Mild parenchymatous nephritis	...	..	0.120	
209	35	Chronic	Negative	145	..	0.180	Marked ascites two weeks' duration. Tuberculous peritonitis. Temp. 102 F.

TABLE 18.—Diabetes Mellitus

No.	Age	Sugar, Per Cent.	Diacetic Acetone	Kidney	Blood Pressure	Phthalein, Per Cent.	Blood Urea	Remarks
9	43	5	Present	Negative	130	..	0.264	
		Neg.	Negative	Negative	...	..	0.120	Carbohydrate free diet.
14	54	T.	Negative	Negative	180	..	0.162	
20	57	2	Negative	Mild chronic interstitial nephritis	154	..	0.150	Sugar free on 60 gm. white bread.
48	51	0.5	Negative	Chronic interstitial nephritis	168	55	0.144	Four years' duration. Mild arteriosclerosis.
172	58	1.3	Present	Chronic interstitial nephritis	...	..	0.362	Gangrene foot.
184	42	5	Present	Chronic interstitial nephritis	150	75	0.336	
		5	Present	Chronic interstitial nephritis	150	..	2.340	In coma. Died on following day.
202	54	5	Present	Chronic interstitial nephritis	242	65	0.300	

TABLE 19.—Diseases of Thyroid

No.	Age	Diagnosis	Kidney	Blood Pressure	Phthalein, Per Cent.	Blood Urea	Remarks
72	20	Exophthalmic goiter	Negative	120	82 62	0.264 0.324 0.180	Before operation 3/25 15. Shortly after operation 3 30 15. After operation 4/5/15.
65	32	Exophthalmic goiter	Negative	110	74	0.240 0.144 0.120	Before operation 3/15/15. After operation 3/20/15. After operation (leaving hospital) 3/30/15.
30	32	Exophthalmic goiter	Negative	135	55	0.276	Before operation.
3	50	Hypothyroidism. Arteriosclerosis	Arteriosclerotic kidney	250	..	0.096 0.118	
160	31	Colloid goiter	Negative	170	..	0.504	Having thyroid extract treatment for six months. Weakness, dyspnea and tachycardia.

TABLE 20.—Malignancy

No.	Age	Diagnosis	Kidney	Blood Pressure	Blood Urea	Urea Fluid	Remarks
55	60	Recurrent papilloma of ovary	Negative	...	0.262	0.426 0.480	Ascites. Palpable abdominal mass.
90	28	Malignant pleura		136	0.204	0.240	
91	40	Adenocarcinoma stomach	Mild parenchymatous nephritis	...	.....	0.204 0.258 0.348	Ascites. Jaundice. Taken just before death.
128	50	Extensive carcinoma of face	Negative	150	0.276	.....	Wassermann.
150	58	Adenocarcinoma stomach	Negative	115	0.648	.....	Before operation. Persistent vomiting.
207	50	Sarcoma of hip	Negative	160	0.408	.....	Before operation.

TABLE 21. MISCELLANEOUS

No.	Age	Diagnosis	Kidney	Blood Pressure	Phthalein, Per Cent.	Blood Urea	Fluid Urea	Remarks
12	55	Acute obstruction (malignant)	Acute toxic nephritis			1.380		Died one day later. Indicanuria.
13	29	Acute obstruction (? etiology)	Negative			0.336		2/1/15. Condition good.
						1.080		2/3/15. After operation
						0.714		2/6/15. Died two days later.
17	46	Acute obstruction. Incarcerated hernia	Negative	115		0.360		2/5/15.
						0.246		2/12/15. Six days after operation. Recovery.
25	26	Psoriasis	Negative	123		0.168		Chronic.
53	23	Urticaria				0.336		First day of rash.
81	38	Pityriasis rosea	Negative	125		0.240		Fourth day of rash.
61	21	Second degree burn (steam)	Negative			0.132	0.108	Two days' duration.
100	15	Second degree burn (gas)	Negative			0.288	0.240	Three days' duration.
19	38	Fractured skull	Negative	110		0.284		2/8/15. One day after injury.
			Glucose T.			0.300		2/11/15. No coma.
96	46	Cerebral hemorrhage	Alb. L. A.	190		0.396		Blood pressure raised 70 m.m. in 2 hours
				260				Death five hours after hemorrhage.
116	28	Concussion	Negative	136		0.456		Patient comatose
						0.336		Fourteen days later, conscious.
78	54	Gout	Negative	130	67	0.288		
144	39	Obstruction common duct (postoperative)	Alb. T	125	13	1.512		5/10. Complete obstruction.
			Many casts			1.560		5/11. Vomiting, not severe.
			Alb. T.	138	20	0.936		5/14. Duct opens.
			Occ. hy. cast		56	0.168		5/29.
						0.144		6/2.
159	51	Obstruction common duct (postoperative)	Negative (bile)		60	0.408		Jaundice
69	39	Epilepsy	Negative	108		0.156		Attack grand mal day previous.
97	56	Traumatic pleurisy	Negative	150	T.	0.354		General anasarca; marked cyanosis.
						0.486		0.540 pleuritic fluid urea. Died four days later
112	24	Esophageal stenosis. Gunshot wound	Negative	88		2.268		Gastrostomy done six days previously.
						2.436		Marked anemia. Died same day urea was taken.
140	46	Intracranial tumor	Negative	152		0.240		Choked disk, extra-ocular palsy, headache. Wassermann negative. Marked ankle clonus. Hyper K. K.
				145				
						0.276		Comatose three days later.
148	24	Chronic arthritis	Negative	132		0.324		
153	54	Arteriosclerosis	Arteriosclerotic	190		0.264		Menopause.
167	23	Bone cyst (jaw)	Negative			0.336		Wassermann negative.
180	43	Neurosis	Negative	140		0.180		Mild arteriosclerosis
194	40	Aneurysm	Negative	102 L. 145 R.		0.262		Large sac arch of aorta. One year's duration.
208	60	Arteriosclerosis	Negative	240		0.360		Diplopia and headache.

DISEASES OF THE THYROID

We made blood urea determinations on three cases of exophthalmic goiter. All showed a urea slightly above normal before operation. Following operation the urea dropped to normal. We studied only one case of myxedema. The patient had in addition marked arteriosclerosis. Two determinations of urea were made, both of which were slightly below normal.

Case 160 was a patient with a large colloid goiter who had taken thyroid extract for six months. He showed marked hyperthyroidism. His blood urea was increased to 0.504 gm. per liter.

The phenolsulphonephthalein output in all three cases of exophthalmic goiter was normal or slightly increased in amount.

MALIGNANCY

A series of six cases was studied, the results of which are shown in Table 20. Two cases show slight increase. Cases 150 and 207 show a distinct elevation, 0.648 and 0.408 gm. per liter, respectively. Neither case had any clinical evidence of nephritis. This observation is not in accord with the conclusion of Tileston and Comfort, who stated that no changes were met with in malignant disease which could not be ascribed to a complicating renal disease.

MISCELLANEOUS

We have studied twenty-four miscellaneous conditions. Four cases of intestinal obstruction had an increased blood urea. Cases 12 and 13 showed very high values, 1.380 and 1.080 gm. per liter, respectively. One case of obstructed bile duct, complicated with parenchymatous nephritis, showed 1.560 gm. per liter, but dropped promptly to normal as soon as the obstruction was relieved. Case 112 gave marked urea increase, 2.311 gm. per liter. The patient had an esophageal stenosis.

Slightly raised values were found in urticaria, fracture of the skull, cerebral hemorrhage, cerebral concussion, traumatic pleurisy, bone cyst, arteriosclerosis, and chronic arthritis. Normal values were obtained in psoriasis, pityriasis rosea, epilepsy, and a functional neurosis.

THE UREA CONTENT OF BODY FLUIDS

A most excellent summary of the literature on the subject is included in the work of Soper and Granat (1914). To that article the reader is referred.

Soper and Granat studied the urea content in the spinal fluid in ninety-seven cases. They found that the amount of the urea in the spinal fluid usually agreed with that in the blood. Most of the variations were due to the difference in time of taking of the fluids.

TABLE 22.—Urea Content in Body Fluids

No.	Diagnosis	Fluid	Fluid Urea	Blood Urea
51	Chronic nephritis	Spinal	0.166	0.210
84	? Syphilis	Spinal	0.324	0.312
74	Paresis	Spinal	0.270	.....
54	Syphilis	Spinal	0.390	0.540
79	Syphilis	Spinal	0.258	0.228
66	Syphilis	Spinal	0.120	0.144
125	Paresis	Spinal	0.204	0.198
126	Meningitis	Spinal	0.324	0.370
130	Meningitis	Spinal	0.255	0.288
140	? Brain tumor	Spinal	0.204	0.240
130	Meningitis	Spinal	0.180	.....
162	Cerebrospinal syphilis	Spinal	0.135	0.240
130	Meningitis	Spinal	0.120	.....
183	Chronic nephritis	Spinal	0.240	0.204
187	Meningitis	Spinal	0.798	0.384
191	Chronic nephritis	Spinal	0.596	0.396
198	Tabes dorsalis	Spinal	0.264	0.276
89	Syphilis	Spinal	0.216	0.180
210	Bulbar paralysis	Spinal	0.120	.....
55	Ovarian tumor (malignant)	Peritoneal	0.426	0.262
91	Carcinoma of stomach	Peritoneal	0.204	.....
91	Carcinoma of stomach	Peritoneal	0.258	.....
91	Carcinoma of stomach	Peritoneal	0.348	.....
55	Ovarian tumor	Peritoneal	0.480	.....
209	Tubercular peritonitis	Peritoneal	0.180	0.180
57	Ovarian tumor	Cyst	0.432	0.233
131	Ovarian tumor	Cyst	0.216	0.192
137	Ovarian tumor	Cyst	0.168	0.156
45	Hydrocele	.....	0.276	0.340
120	Hydrocele	.....	0.484	.....
61	Second degree burn	Vesicle	0.108	0.132
100	Second degree burn	Vesicle	0.242	0.288
27	Pleurisy	Pleural	0.540	0.486
90	Malignant pleura	Pleural	0.240	0.204
115	Anemia	Pericardial	1.680	1.778
211	Gonorrheal arthritis	Joint fluid	0.240	0.240

TABLE 23.—PHTHALEINS

Case Number	Per Cent. Phthalein 2 Hrs.	Blood Urea	Case Number	Per Cent. Phthalein 2 Hrs.	Blood Urea
196	65	0.108	202	65	0.306
41	82	0.120	29	70	0.306
6	65	0.120	84	60	0.312
197	70	0.120	99	57	0.312
40	67	0.156	80	60	0.326
59	67	0.156	33	75	0.324
137	82	0.156	85	42	0.324
77	65	0.160	134	80	0.324
165	68	0.168	92	70	0.336
144	56	0.168	107	45	0.336
38	72	0.168	116	67	0.336
39	87	0.168	169	78	0.336
44	75	0.168	175	80	0.336
48	55	0.144	156	75	0.336
5	15	0.180	184	75	0.336
60	40	0.180	45	67	0.340
63	72	0.180	27	T	0.354
106	55	0.180	68	54	0.360
109	82	0.180	95	37	0.360
132	66	0.182	122	62	0.360
58	50	0.192	151	38	0.360
131	68	0.192	136	77	0.360
125	15	0.198	182	80	0.372
183	67	0.204	76	50	0.396
195	50	0.204	28	55	0.408
83	60	0.216	159	60	0.408
82	42	0.222	73	37	0.420
162	73	0.240	164	63	0.420
105	70	0.242	70	40	0.432
176	82	0.252	139	T	0.438
190	95	0.256	163	64	0.444
130	65	0.228	31	67	0.456
64	50	0.264	97	25	0.444
71	82	0.264	51	47	0.480
101	65	0.264	156	38	0.516
68	30	0.264	54	37	0.540
180	62	0.264	105	60	0.546
30	55	0.276	178	68	0.552

TABLE 23 PHTHALEINS (*Continued*)

Case Number	Per Cent. Phthalein 2 Hrs.	Blood Urea	Case Number	Per Cent. Phthalein 2 Hrs.	Blood Urea
32	63	0.270	121	T	0.600
10	70	0.276	71	22	0.624
35	65	0.280	181	70	0.636
50	77	0.288	156	30	0.672
78	67	0.288	1	15	0.694
87	42	0.288	156	26	0.720
123	87	0.288	144	20	0.936
172	T	0.285	4	20	1.008
11	95	0.294	144	13	1.560
193	70	0.300	108	T	3.360

They quote the work of Javal as establishing the fact that the urea content of body fluids, edema, pleural and ascitic, equals in amount the blood urea. They found the normal urea in spinal fluid between 0.01 per cent. and 0.05 per cent.

Cullen and Ellis[36] (1915) have shown that when the blood and spinal fluid are drawn at about the same time the difference in the amount of urea in the two fluids is rarely greater than 2 mg. per 100 c.c.

We have made comparative urea determinations on the body fluids and blood of twenty-eight different patients. Of these nineteen were spinal and six were peritoneal fluids. Table 23 shows the results, and they will be seen to correspond closely with those obtained by Soper and Granat. In the main the blood urea equals the fluid urea. Cases 54, 55, 57, 187 and 191 show rather marked differences. The fluids and blood from Cases 54, 55 and 57 were taken within a few minutes of each other. The fluids from Cases 55 and 57 were from very thick-walled ovarian cysts. The fluids from Cases 187 and 191 were taken at different times from the blood.

CONCLUSIONS

1. In the normal fasting adult the blood urea varied from 0.108 to 0.252 gm. per liter.

2. The majority of cases of acute nephritis show an increased urea.

3. In mild chronic nephritis there is a normal or slightly elevated amount of blood urea. Cases of advanced chronic nephritis have a distinct increase. The effect of an associated cardiac decompensation is to further elevate the blood urea.

36. Cullen and Ellis: Jour. Biol. Chem., 1915, xx, 511.

TABLE 24.—Blood Pressures *

Case No.	Age	Blood Pressure	Blood Urea	Case No.	Age	Blood Pressure	Blood Urea
110	51	68	0.708	122	43	112	0.360
37	36	80	0.168	122	43	112	0.456
106	28	88	0.180	138	35	112	0.242
112	23	88	2.316	150	58	112	0.648
106	28	90	0.156	163	30	112	0.444
59	34	92	0.156	17	46	115	0.246
115	8	92	0.596	89	25	115	0.180
87	43	94	0.384	99	34	115	0.312
182	60	96	0.372	23	35	116	0.390
97	53	98	0.336	47	24	116	0.192
123	45	100	0.288	92	27	117	0.336
122	43	100	0.408	34	48	118	0.480
164	29	100	0.420	119	28	118	0.144
33	17	100	0.324	130	53	118	0.228
38	23	100	0.168	135	40	118	0.312
58	22	100	0.192	146	..	118	0.276
39	21	102	0.168	173	46	118	0.300
70	28	102	0.120	31	60	119	0.456
107	45	102	0.336	32	20	119	0.270
175	25	102	0.336	24	40	120	0.150
193	45	103	0.300	29	..	120	0.336
168	50	104	0.132	21	41	120	0.222
36	44	104	0.660	72	20	120	0.264
142	..	105	0.288	95	27	120	0.360
137	25	106	0.156	97	53	120	0.444
54	34	108	0.540	101	55	120	0.264
62	39	108	0.156	145	..	120	0.336
169	40	108	0.336	158	56	120	0.276
19	38	110	0.384	162	24	120	0.240
35	23	110	0.280	170	32	120	0.120
69	21	110	0.108	178	39	120	0.552
70	28	110	0.432	195	20	120	0.204
73	34	110	0.420	197	23	120	0.120
121	..	110	0.600	198	41	120	0.276
133	14	110	0.255	200	32	120	0.216
151	37	110	0.360	201	..	120	0.204
122	43	110	0.300	40	21	122	0.156
11	..	112	0.288	41	21	122	0.120

* Blood pressures are systolic.

TABLE 24.—Blood Pressures*—(*Continued*)

Case No.	Age	Blood Pressure	Blood Urea	Case No.	Age	Blood Pressure	Blood Urea
50	67	122	0.288	151	37	140	0.660
88	28	122	0.180	171	18	140	0.168
148	..	122	0.394	181	42	140	0.636
176	..	122	0.252	189	43	140	0.180
25	26	123	0.168	190	45	140	0.256
81	38	125	0.216	104	..	142	0.204
144	39	125	1.512	109	47	142	0.180
60	22	126	0.180	130	53	142	0.180
68	50	126	0.360	157	45	142	0.348
103	..	126	0.192	166	22	144	0.225
205	35	128	0.210	113	26	145	0.324
129	33	130	0.360	140	46	145	0.276
156	32	130	0.672	194	..	145	0.264
26	22	130	0.252	200	35	145	0.180
78	54	130	0.288	67	40	148	0.156
79	57	130	0.228	126	35	148	0.370
102	35	130	0.336	7	72	150	0.084
140	46	132	0.240	22	16	150	0.372
139	62	132	0.438	84	42	150	0.312
144	39	132	1.560	128	50	150	0.276
9	43	130	0.264	184	42	150	0.336
188	45	130	0.180	108	47	152	3.360
196	26	132	0.108	27	56	150	0.354
206	34	132	0.360	16	33	154	0.324
204	60	132	0.216	20	67	154	0.150
23	33	134	0.408	10	54	154	0.276
127	65	134	0.240	131	37	154	0.192
156	32	134	0.720	124	24	155	0.264
8	54	135	0.210	15	27	156	0.228
30	32	135	0.276	116	28	156	0.426
155	34	135	0.240	207	50	160	0.408
90	28	136	0.204	134	47	162	1.080
6	48	137	0.120	136	33	162	0.480
75	80	137	0.264	165	64	162	0.168
105	47	138	0.546	48	51	168	0.144
180	34	138	0.264	114	60	168	0.324
149	50	140	0.312	203	68	168	0.380
68	50	140	0.264	86	46	170	0.348

TABLE 24.—Blood Pressures*—(*Continued*)

Case No.	Age	Blood Pressure	Blood Urea	Case No.	Age	Blood Pressure	Blood Urea
141	54	170	0.420	80	46	190	0.396
160	31	170	0.504	153	54	190	0.264
199	42	172	0.180	191	58	204	0.396
47	..	178	0.242	85	60	208	0.324
14	57	180	0.150	143	69	220	0.480
44	56	180	0.168	18	55	230	0.276
132	46	180	0.182	56	65	240	0.414
105	47	180	0.242	208	60	240	0.360
152	62	185	0.285	161	56	242	0.336
174	67	186	0.264	22	54	242	0.300
	75	190	0.694	3	50	250	0.096
4	78	190	1.008	5	26	250	0.240
46	55	190	0.288	76	29	250	0.396

4. A high value occurring with a transient mechanical obstruction of the urinary tract does not necessarily mean a bad prognosis.

5. In polycystic kidneys, with a very large amount of blood urea, and low phthalein excretion, the outcome may not be immediately fatal.

6. The majority of cases of lobar pneumonia have a raised value. A bad prognosis should be given in those cases which show considerable increase.

7. Approximately one-half of the cases of syphilis show a distinct elevation.

8. In exophthalmic goiter there is an increase, and in myxedema, a decrease in blood urea.

9. In primary anemia, nephrolithiasis, pyelonephritis, pyonephrosis, septicemia, streptococcic meningitis, Rocky Mountain spotted fever, pulmonary tuberculosis, diabetic coma, intestinal obstruction, malignancy, and common duct obstruction, we find a definite increase in most of the cases.

10. A slight elevation occurs in valvular heart lesions, myocarditis, secondary anemia, urticaria, fractured skull, cerebral hemorrhage, concussion, bone cyst, traumatic pleurisy, arteriosclerosis and chronic arthritis.

11. No changes were found in psoriasis, pityriasis rosea, epilepsy, meningococcic meningitis, diabetes and functional neurosis.

12. The urea content of body fluids, in the majority of cases, agrees with the blood urea.

13. The blood pressure was taken in 178 cases. Reference to the results, as given in Table 24, will readily show that there is no relation between blood pressure and the amount of blood urea.

14. The results of phthalein excretion in ninety-six cases agree with the observation of others, who find in most cases the percentage of phthalein excreted is diminished along with increase in blood urea (Table 23).

THE EFFECT OF CONTINUOUS ELECTRIC LIGHT IN EXPERIMENTAL ARTHRITIS*

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It has been observed that a patient suffering from rheumatic pains and joints is very often relieved by the application of incandescent light either locally by means of one, two, or three bulbs with a metal reflector, or by a more general application in the form of the electric light bath. Although much is written in the literature on light as a therapeutic agent, we have been unable to find any previous work done to bring out experimentally this particular phase of treatment.

The following is the report of a study of experimental arthritis in rabbits and its treatment by means of the incandescent electric light.

Preliminary standardizations were made to ascertain: (1) The amount of light that could be used on a normal rabbit without causing distress, loss of weight, or an increase in temperature; (2) the dosage of an organism that would produce in all cases an arthritis in from five to seven days; and (3) the size of rabbit best suited for bringing out the factors selected for study.

The first three series of rabbits were treated in a cage having glass sides, metal door and top, lighted continuously by two or three electric globes of the Edison Mazda, 110 volt, 150 watt type. The electric globes were suspended within the cage, giving a temperature of 15 to 20 degrees centigrade above the outside atmosphere or an average of 35 C. The fourth and fifth series were treated in open wire cages allowing free circulation of air on all sides. In these series the temperature was but 4 to 6 degrees higher than that of the surrounding atmosphere. The organism used was the *Streptococcus haemolyticus,* isolated from the crypts of the tonsils after removal, following an attack of acute tonsillitis and polyarthritis; dosage, one-fifth of a forty-eight hour blood ager slant growth. The rabbits were about 1,000 gm. in weight.

The factors selected for study were: (a) Number and extent of the joint lesions, (b) weight, (*c*) temperature, (d) leukocyte count.

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* From the Departments of Therapeutics and Experimental Medicine, College of Medicine, University of Illinois.

* Read before the Medical Research Club of the University of Illinois, June 9, 1915

Six rabbits were injected intravenously with the living streptococci. Three were placed in the closed cage, as described, for treatment and the other three in an open wire cage as controls.

Among the treated animals two developed arthritis, one having a single mild involvement, the other three mild lesions, a total of four joints involved. The third rabbit showed no lesion. Of the untreated rabbits, all had arthritis, one had three slight lesions, the second three moderately severe and the third four, a total of ten.

A second similar series showed still better results. Two treated rabbits escaped arthritis and the remaining one had four moderately severe joints. Of the untreated rabbits, one had three severe joints, the second four severe and the third five severe lesions, a comparison of four in the treated to twelve in the untreated animals.

A third series of twelve rabbits gave results of four lesions in six treated animals against ten in six untreated rabbits.

In the next series, the first treated in open wire cages, the dose of living streptococci was slightly increased. Six treated rabbits gave ten joint lesions, three not having lesions. Six untreated had sixteen joint lesions, none of the animals escaping.

In a further series of eight rabbits, four treated gave five lesions and four untreated nine joint lesions. This time the rabbits were not treated until arthritis developed, and then the light treatment was pushed. The treated rabbits improved, while the others continued to have new involvements.

The most reliable factor for study was the actual formation of pathological lesions in and around joints, with impairment of function, pain, swelling or exudation and confirmation of our clinical findings by necropsy.

The joint lesions were classified as mild, moderate or severe. An arthritis was considered as mild when impairment of function and tenderness on palpation were transitory in character and swelling was either absent or of a mild degree; moderate, when impairment of function and tenderness were of longer duration and the enlargement had largely disappeared at necropsy; and severe, when the swelling was readily noticeable, the function entirely lost, and either marked exudation or suppuration present at autopsy in the joint and periarticular tissues.

TABLE SHOWING COMPARISON OF THE TOTAL RESULTS IN TWENTY-TWO TREATED AND TWENTY-TWO UNTREATED RABBITS

	Treated	Untreated
No. of joints involved per rabbit	1.2	2.58
Severe lesions	2.0	11.0
Average gain in weight in grams	65.0	38.25
Average daily temperature	103.3	103.8
Average maximum temperature	104.9	105.5

As will be seen in Table 1, the number of joints involved per rabbit in the twenty-two treated was 1.2 or a total of twenty-seven, two of these being classed as severe. In comparison we find that the untreated animals developed fifty-seven arthritic lesions, or 2.58 per rabbit, over twice as many per animal as in the former group. In further confirmation of this, the untreated animals had eleven severe lesions or five times as many as the treated animals.

In a previous paper[1] by one of the contributors on the prophylactic treatment of experimental arthritis with vaccines, it was observed that the weight curve of the treated animals was more uniform than the weight curve of the untreated. This led to the observation of

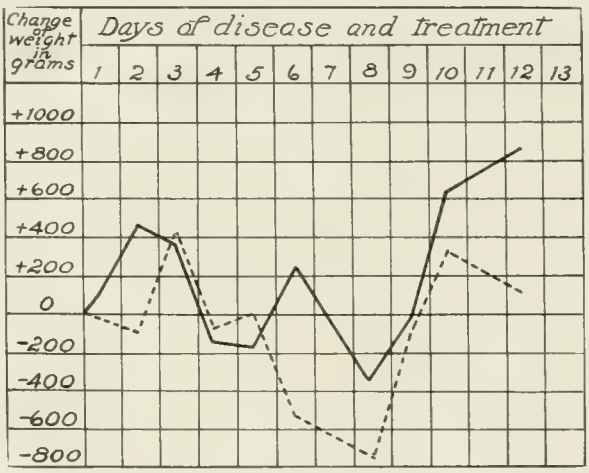

Chart 1.—Composite weight curve of twenty-two treated and twenty-two untreated rabbits. Solid line, treated animals; broken line, untreated animals.

the weight changes in this series of experiments. Somewhat similar results were noted. The rabbits under the rays of the incandescent light gained on an average almost twice as many grams per animal as those untreated, or an average of 65 to 38 gm. All the animals did not gain in weight. There were individual losses in each group, but the total gain favored the treated animals, as shown in Table 1.

To eliminate as many variable factors as possible, the total average gain was based on the weight of the animals at the time of death from the streptococcus infection, or when they were chloroformed for necropsy. The latter period was from two to six weeks after the injection. However, the animals were weighed at regular intervals during the course of the experiments and Chart 1 illustrates much

1. Moore, J. J.: Jour. Infect. Dis., 1914, xv, 215.

better than words the marked variations in the average composite weight curve of the two groups. It will be observed that up to the fifth day the variations are approximately the same, the difference shown being in favor of the untreated animals. After that date, which corresponds with the appearance of arthritic lesions, although the curves are somewhat parallel, there is a great difference in degree. Of the animals living on twelfth day the total composite weight gain for the treated was 837 gm. and for the untreated 142 gm.

Again, the composite temperature curve of the treated animals is not as high as that of the other group, as is illustrated by Chart 2. This is important, as the atmospheric temperature in the cages with the light was usually from 15 to 20 degrees Centigrade higher than in the cages of the controls. Another point of interest is that the

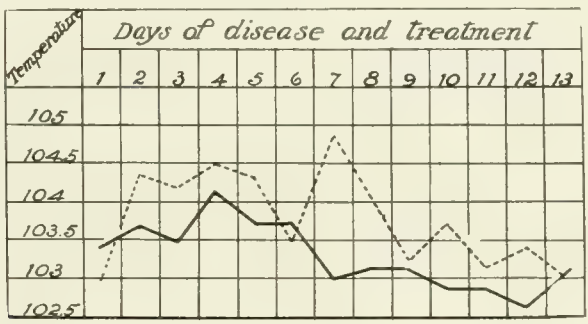

Chart 2.—Composite temperature curve of twenty-two treated and twenty-two untreated rabbits. Solid line, treated animals; broken line, untreated animals.

average maximum temperature of the treated animals was 0.5 degree Fahrenheit lower than the controls, as shown by Table 1. The same variation was found in the average daily temperature of the two groups. The leukocyte count of the two series showed but little variation. The last two series eliminated the heat factor to a considerable extent, the temperature in these experiments being only 4-6 degrees C. above the surrounding temperature.

CONCLUSIONS

The production of experimental arthritis in rabbits was either prevented, or was much milder in degree, in animals treated with the continuous incandescent electric light than in the controls not treated.

Rabbits treated with the incandescent electric light after developing acute experimental arthritis recovered more rapidly than the control animals.

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THE INTRASPINAL TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM, ACCORDING TO THE METHOD OF SWIFT AND ELLIS*

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In 1912 Swift and Ellis[1] described a method for the intraspinal treatment of syphilis of the cerebrospinal axis. They felt that since practically all drugs were excreted into the subarachnoid space either poorly or not at all, a direct application of salvarsan to the meninges would have a distinctly greater curative effect than when salvarsan was given only by the intravenous route. That intraspinal injections of salvarsan or neosalvarsan, dissolved in salt solution, were far too irritating to be practical was shown by their[2] experiments on monkeys. The medium which Swift and Ellis[1, 3] finally decided on was the blood serum of a patient, withdrawn shortly after the intravenous administration of salvarsan. This blood serum, diluted with salt solution, was introduced into the subarachnoid space, without severe symptoms of meningeal irritation and with beneficial results in syphilis. This method has been criticized on the ground that it was unnecessary because the intravenous injection of salvarsan was all-sufficient in its action. In the light of the recent investigations of Adler,[4] Hall,[5] Swift,[6] Camp[7] and others, who have shown that no arsenic, or only the merest trace of it, appears in the spinal fluid after the intravenous administration of salvarsan, it would seem that the direct method is the only way in which arsenic can be introduced into the subarachnoid space in adequate dosage.

Another criticism has been that a therapeutically negligible amount of arsenic was introduced in the "autosalvarsanized" serum. Draper[8] has shown that no more than 0.25 milligram to 0.5 milligram of salvarsan can be introduced repeatedly with safety into the subarachnoid space. Swift[6] and Adler[4] have shown that blood serum, removed a

* Submitted for publication Sept. 9, 1915.

1. Swift, H. F., and Ellis, A. W. M.: New York Med. Jour., July 13, 1912.
2. Ellis, A. W. M., and Swift, Homer F.: Jour. Exper. Med., 1913, xviii, 4.
3. Swift, Homer F., and Ellis, A. W. M.: THE ARCHIVES INT. MED., 1913, xii, 331.
4. Adler, Herman M.: Boston Med. and Surg. Jour., 1914, clxxi, 900.
5. Hall, G. W.: Jour. Am. Med. Assn., April 24, 1915, lxiv, 1384.
6. Swift, H. F.: Jour. Am. Med. Assn., 1915, lxv, 209.
7. Camp: Lancet-Clinic, 1915, cxiii, 116.
8. Draper, George: THE ARCHIVES INT. MED., 1915, xv, 16.

short time after the intravenous administration of salvarsan, contains amounts varying between these limits, and seldom below them.

It would seem, then, that by the intraspinal injection of autosalvarsanized serum we have a method of introducing arsenic in nontoxic doses into the subarachnoid space. Several other methods for the introduction of neosalvarsan and salvarsan into the subarachnoid space have been described, notably that of Ravaut[9] and Wile's[10] modification of this method and that of Ogilvie.[11] A discussion of these methods would be out of place in this paper as we have had no personal experience with them.

Since the communications of Swift and Ellis, numerous reports regarding the efficiency of autosalvarsanized serum in the treatment of syphilis of the central nervous system have appeared. A brief review of them is of considerable interest.

McCaskey[12] gave twenty intraspinal injections to seven patients. His longest observation extended over a period of three months. He states that some of his patients improved very much under treatment. He gives no data as to the effect of the treatment on the laboratory findings. In another article[13] the same author describes some technical modifications of the method, but fails to state whether or not his results were favorable.

Hough[14] treated six paretics. As two of his cases received but one treatment each, his report is based on his results in four cases. Three showed some symptomatic improvement, while all four showed marked improvement in the blood and spinal fluid findings.

Cutting and Mack[15] report their results in six cases of paresis and one case of cerebral syphilis. The mental condition in all but one showed no improvement. There was no marked change in the neurological findings. The cell counts in the spinal fluids showed a constant and marked reduction, although the Wassermann reaction remained positive and there was no effect on the globulin content.

In eight cases of paresis treated by Myerson[16] definite changes were seen in the spinal fluid findings after treatment. No real clinical improvement was seen.

Pillsbury[17] used the intraspinal treatment in eleven cases of advanced paresis. Six of these patients showed improvement either

9. Ravaut, P.: Bull. et mém. Soc. méd. d. hôp. de Paris, 1913, xxxvi, 752.
10. Wile, U. J.: Jour. Am. Med. Assn., 1914, lxii, 1163; ibid., 1914, lxiii, 173.
11. Ogilvie, H. S.: Jour. Am. Med. Assn., Nov 28, 1914, lxiii, 1936.
12. McCaskey, G. W.: Jour. Am. Med. Assn., 1914, lxii, 187.
13. McCaskey, G. W.: Jour. Am. Med. Assn., 1914, lxii, 1709.
14. Hough, W. H.: Jour. Am. Med. Assn., 1914, lxii, 183.
15. Cutting and Mack: Jour. Am. Med. Assn., 1914, lxii, 903.
16. Myerson: Boston Med. and Surg. Jour., May 7, 1914.
17. Pillsbury, L. B.: Jour. Am. Med. Assn., 1914, lxiii, 15.

in the clinical condition or in the laboratory findings. There was only one case which showed decided clinical improvement.

Mapother and Beaton[18] report their results in four cases of early paresis. They gave five combined intravenous and intraspinous treatments to each patient. There were no appreciable changes noted in the mental condition of the patients. No changes in the blood and spinal fluid Wassermann reactions, which were performed quantitatively, were seen. The pleocytosis and increased globulin content remained unaffected in all cases.

Riggs and Hammes[19] gave 100 intraspinal treatments to twenty-four patients. In each patient who received over four combined injections the blood Wassermann reaction became negative, except in one case of juvenile paresis. The blood and spinal fluid findings became normal in every way in 75 per cent. of the cases of tabes thus treated. These changes were accompanied by marked clinical improvement. In paresis the results of treatment were less encouraging. The clinical improvement was rarely marked even after a great deal of treatment had been given.

Litterer[20] reports a series of four cases of paresis and eleven cases of tabes or cerebrospinal syphilis in which the intraspinal injections were used. Ten of the paretics showed improvement. All the cases of cerebrospinal syphilis and of tabes showed marked betterment. Four had had a great deal of salvarsan or neosalvarsan intravenously with no more than temporary improvement of their symptoms.

McClure[21] treated four cases of cerebrospinal syphilis, two of tabes dorsalis, one of taboparesis and two of paresis, a total of nine cases. None of his cases were observed for a longer period than five months. All the cases of tabes and cerebrospinal syphilis showed definite improvement, both clinical and in the laboratory findings. One case of paresis showed no improvement, while the other improved greatly.

Krida[22] has given seventy-two intraspinal injections in eighteen cases. Out of eight cases of tabes there were four which showed improvement and four which failed to improve. In four cases of paresis there was no improvement in the mental symptoms. One paretic died after an intraspinal injection.

Ayer[23] has reported his results in sixteen cases. His report is of great value on account of the length of time over which he was able

18. Mapother, E., and Beaton, T.: Lancet, London, 1914, clxxxvi, 1103.
19. Riggs and Hammes: Jour. Am. Med. Assn., 1914, lxiii, 1277.
20. Litterer, W.: Lancet-Clinic, 1915, cxiii, 359.
21. McClure, C. W.: Boston Med. and Surg. Jour., 1914, clxxi, 520.
22. Krida: Albany Med. Ann., 1914, xxxv, 243.
23. Ayer, James B.: Boston Med. and Surg. Jour., 1914, clxx, 452.

to observe his patients. The shortest observation is for a period of thirteen months. His most flattering results were in cerebrospinal syphilis, in which condition Ayer believes that persistent treatment in favorable instances, will accomplish a cure. In tabes he believes that an arrest of the process is often to be expected. His results in paresis were far less satisfactory.

Draper,[8] continuing the observations on Swift and Ellis' original series, reports his results in a series of twenty-five cases. The report is exceptionally careful and detailed. The series includes conditions ranging from tabes associated with painful crises up to brain involvements with marked mental disturbance. There was marked clinical improvement in all classes. The pain and ataxia were usually greatly relieved. Those with bulbar involvement or with mental disturbance showed much improvement, not only in the symptoms, but in the laboratory evidences of the disease. He found that there was apparently no limit to the number of intraspinal injections which might be given when the autosalvarsanized serum was used.

Smith[24] gave fifty-three injections to twelve patients. In some of his cases, however, he injected undiluted blood serum into the subarachnoid space. In this point only did his technic differ from the original Swift-Ellis method. He used Wile's modification of the Ravaut method fourteen times in twelve additional cases. With this latter method he had unfortunate results, and concludes that it is too dangerous to use. His results with the Swift-Ellis technic were excellent. Clinically, he found marked improvement, and the serological findings in the spinal fluid either diminished or returned to normal. The pleocytosis in the spinal fluid was affected first, next the Wassermann reaction was diminished, but the increased globulin content was the slowest of the three tests to disappear.

The general conclusion which can be drawn from the above reports indicates that by this method some changes may occur in paresis, but that much permanent improvement is scarcely to be expected. On the other hand, the effect of the treatment in cerebrospinal syphilis and tabes dorsalis seems to be extremely beneficial. The symptomatic improvement is often marked and a diminution or a complete disappearance of the serological findings in both the blood and the spinal fluid may be expected in most instances.

The method has been criticized on the ground that it is dangerous. A careful search of the literature shows the following fatalities:

Lorenz[25] treated five patients with paresis. Two died. He then gave up this particular technic, stating that it "has in our hands been

24. Smith, L. D.: Jour. Am. Med. Assn., 1915, lxiv, 1563.
25. Lorenz: Wisconsin Med. Jour., 1913, xii, 171.

very irritating and caused alarming symptoms." Pillsbury[17] reports the death of a paretic shortly after an intradural treatment. Krida[22] also reported the death of a paretic. Neither Swift and Ellis,[1, 3] Ayer,[23] Draper,[8] nor Smith[24] have had a fatality in their extensive series. It is noteworthy that the reported deaths have been among paretics, and that no fatalities have occurred after the treatment of tabetics. The number of fatalities in the total number of treatments is not alarming, considering the desperate outlook in this condition. No account is taken of fatalities occurring after any kind of intradural treatment except that of Swift and Ellis.

We wish to report our results with the intraspinal injection of autosalvarsanized serum in syphilitic affections of the central nervous system. The number of our cases is limited but the value of our report may be increased by the length of time that some of them have been under observation. Our first patient came under treatment in January, 1913, and the second one a short time later (March, 1913). These two patients were under our care so short a time that they are scarcely worthy of consideration.

In addition to these two preliminary cases we have observed one case of extremely acute cerebrospinal syphilis, eight cases of definite tabes or cerebrospinal syphilis and one case of paresis.

We have followed rigidly the Swift-Ellis technic. From one-half hour to one hour after an intravenous injection of salvarsan or neosalvarsan from 40 to 50 c.c. of blood are withdrawn with aseptic precautions from the patient by venipuncture, using a McRae needle fitted to a 50 c.c. centrifuge tube. The tube is then corked with a sterile cork, and after the blood has clotted, the clot is separated from the sides of the tube with a sterile platinum wire. The serum is then separated in a rapid centrifuge, then withdrawn with a sterile capillary pipet and ejected into a sterile, graduated, glass-stoppered mixing cylinder. Especial care must be taken to have the serum absolutely free from red blood cells and fibrin. Sufficient sterile normal sodium chlorid solution is added to make the desired dilution, the cylinder is stoppered and is placed in a water bath at 56 C. for one-half hour. On the following day lumbar puncture is performed. Fifteen c.c. of spinal fluid are allowed to run out into a graduated test tube, when the barrel of a 25 c.c. Luer syringe is attached to the free end of the lumbar puncture needle by the intervention of a section of rubber tubing 12 inches long, fitted with slip-joint connections. When the spinal fluid appears in the syringe (which is held upright so that it may be used as a graduated funnel) the serum mixture is poured in it. This is allowed to flow by gravity.

ABSTRACT OF CASE HISTORIES

An abstract of the histories of these cases follows:

CASE 1.—(Table 1.) W. I. S. Cerebrospinal syphilis. Male, 29 years old. Married. The intraspinous treatment was begun March 13, 1913. The year before the patient consulted us he had been temporarily unable to void urine and had had to be catheterized. Five months later he began to have shooting pains in the legs which were thought to be sciatica. Attacks of pain in the

TABLE 1.—(CASE 1.) CEREBROSPINAL SYPHILIS

W. I. S., aged 29. Cerebrospinal syphilis. Duration: one year. Syphilis admitted. Result: marked improvement.

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intravenous Salvarsan gm.	Serum Intraspinously c.c.	pct.
		Cells per c.mm.	Noguchi Globulin Test	Wassermann Reaction No. c.c.			
2/ 7/13	+++	153	++	0.1, ++ 0.2, +++	.....	.....	
2/13/13	.....	.....	.....	.....	914, 0.3	.....	
2/26/13	.....	.....	.....	.....	914, 0.5	.....	
3/13/13	.....	.....	.....	.....	914, 0.6	.....	
3/14/13 *	—	16	+	0.3, +++	.....	20	40
5/14/13	.....	.....	.....	.....	914, 0.6	.....	
5/15/13	.....	.....	.....	0.3, +++	.....	25	40
6/22/13 †	.....	.....	.....	.....	914, 0.6	.....	
7/ 8/13	.....	.....	.....	.....	606, 0.6	.....	
7/10/13	.....	0	—	0.3, ++ 0.4, +++	.....	25	40
8/21/13	.....	.....	.....	.....	606, 0.5	.....	
8/22/13	.....	.....	.....	0.2, + 0.3, +++	.....	25	40
10/ 3/13	.....	.....	.....	.....	606, 0.55	.....	
10/16/13	.....	.....	.....	.....	606, 0.55	.....	
12/ 1/13 ‡	.....	.....	.....	.....	606, 0.5	.....	
12/ 3/13	—	3.3	—	0.5, — 1.0, +++	.....	22	40
1/26/14	.....	.....	.....	.....	606, 0.5	.....	
1/27/14	.....	13	—	0.5, — 1.0, +++	.....	25	40
2/ 8/14	± ++	.....	.....	.....	.....	.....	
3/26/14	.....	.....	.....	.....	606, 0.5	.....	
3/27/14	.....	3	±	0.8, +++	.....	25	50

*Patient has been having $HgCl_2$ injections.
† General condition poor. Luetic orchitis.
‡ General condition much improved.

legs and abdomen were a frequent occurrence. Diplopia and ptosis of the left eyelid appeared three weeks before he was seen by us. At examination the pupils reacted sluggishly to both light and accommodation and were unequal in outline. The knee and ankle jerks were absent. The sensations of touch, pain, heat and cold were diminished all over the body except on the face and neck. The blood showed a very strongly positive Wassermann reaction. The spinal

fluid showed a great globulin increase, 153 cells to the c.mm., and a Wassermann reaction strongly positive with 0.2 c.c. of the fluid. The process was advancing rapidly, for between the time of the first examination and the first treatment, a period of nineteen days, he grew rapidly worse. It was almost impossible for him to get about on account of an ever increasing paresis of the right leg.

The improvement was very slow in this case. His general condition was poor and he had a complicating luetic orchitis. It was not until he had received eight intravenous injections and four intraspinous injections, stretching over eight months, that he reported himself as being free from pain in the legs, and suffered only an occasional twinge in the chest. His improvement has been steady since that time. His last treatment was in March, 1914.

Summary of Treatment.—This patient has been under observation over two years. In that time he has received twelve intravenous injections of salvarsan (a total of 5.4 gm.) and seven intraspinal injections. Further, he has received much mercury, both by injection and by inunction.

Results and Present Condition.—In May, 1915, the patient reported that he had had only one attack of pain in the last year. He has returned to his business, which he is pursuing as usual. He has regained the power in his right leg and he walks perfectly well. The physical findings are much the same as when he was first observed, except that the sensations have returned to a marked degree. There has been marked improvment in the laboratory findings in both the blood and spinal fluid.

Case 2.—(Table 2.) W. M. B. Moderately advance tabes. Male, 45 years old. Single. The intraspinous treatment was begun May 8, 1913. The patient was infected with syphilis at the age of 25. He walked unsteadily and had attacks of lancinating pains in the legs for two years previous to the time at which he was first seen by us. He had had three intravenous injections of salvarsan (0.6 gm. each) before consulting us. At examination, the pupils were unequal but reacted to light and accommodation. The knee and ankle jerks were absent. There was a large area of hypalgesia over the outside of the left thigh. Romberg's sign was present. The Wassermann reaction in the blood was strongly positive. The spinal fluid showed a moderately increased globulin content, 75 cells per c.mm., and a Wassermann positive in 0.1 c.c. of spinal fluid.

After seven injections of neosalvarsan and five intraspinal injections the laboratory findings showed decided improvement. The globulin disappeared and the cell count was reduced from 75 to 5 per c.mm. Sensory changes were less marked and the patient walked better. It is interesting to note that the lancinating pains in this case disappeared after the first intraspinal treatment and have never returned. The patient was then put on mercurial inunctions, and after a short time he became very uncertain on his feet and had much increased numbness and tingling, so much so that he could not walk without assistance. The mercury was discontinued and he received four intravenous injections of salvarsan and one intraspinal injection with a very marked improvement in his ability to walk.

After receiving eighteen intravenous injections and fourteen intraspinal injections, the patient was so much improved that he went west and took up his duties as a ranch owner, performing all the duties of ranch life, walking, driving, riding, plowing and so forth, without difficulty.

He returned, after an absence of ten months, when we found his blood Wassermann reaction negative. The globulin content of the spinal fluid was not increased. The cells were within normal limits and the Wassermann reaction was strongly positive only when 0.5 c.c. of fluid was used.

Summary of Treatment.—This patient was under observation over two years. He has received in all twenty intravenous injections of salvarsan or neosalvarsan (the equivalent of 10.7 gm. salvarsan) and fifteen intraspinal injections. He had practically no reaction after either form of treatment.

TABLE 2.—(Case 2.) Tabes Dorsalis

W. M. B., aged 45. Moderately advanced tabes dorsalis. Duration: two years. Syphilis admitted. Result: marked improvement.

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intravenous Salvarsan gm.	Serum Intraspinously
		Cells per c.mm.	Noguchi Globulin Test	Wassermann Reaction No. c.c.		c.c. pct.
5/ 2/13	+++	75	.....	0.1, +++	.....	.....
5/ 7/13	.....	.....	.....	.....	914, 0.6	.....
5/18/13	.....	.....	.....	.....	914, 0.6	.....
5/19/13	.....	.....	.....	.....	.....	25 40
6/ 3/13	.....	.....	.....	.....	914, 0.6	.....
6/ 4/13	.....	20	+	0.1, +++	.....	25 40
6/18/13	.....	.....	.....	.....	914, 0.6	.....
6/19/13	.....	10	+	0.1, +++	.....	25 40
7/ 1/13	.....	.....	.....	.....	914, 0.9	.....
7/ 2/13	.....	5	—	.....	.....	25 40
7/16/13	.....	.....	.....	.....	914, 0.9	.....
7/17/13	.....	.....	.....	0.2, +++	.....	25 40
7/31/13	.....	.....	.....	.....	914, 0.9	.....
8/ 6/13	Pupils equ	al Hypal	gesia less.	.....	.....	.....
8/27/13	Used Hg	rubs. Sensa	tion dulled.	.....	.....	.....
9/12/13	+++	1	—	0.2, +	.....	.....
				0.3, +++		
9/15/13	.....	.....	.....	.....	606, 0.5	.....
9/29/13	.....	.....	.....	.....	606, 0.5	.....
10/13/13	.....	.....	.....	.....	606, 0.5	.....
11/ 1/13	+++	.....	.....	.....	.....	.....
11/ 6/13	.....	.....	.....	.....	606, 0.5	.....
11/ 7/13	.....	10	—	0.1, +++	.....	25 40
11/17/13	Numbness	gone. Sen	sation eve	rywhere	acute.	.....
12/ 1/13*	.....	.....	.....	.....	606, 0.5	.....
12/ 2/13	.....	6	.....	0.3, +++	.....	25 40
1/ 8/14	.....	.....	.....	.....	606, 0.6	.....
1/ 9/14	.....	0	—	0.2, +++	.....	25 40
2/ 5/14	.....	.....	.....	.....	606, 0.6	.....
2/ 6/14	.....	.....	.....	0.3, +++	.....	25 40
2/19/14	.....	.....	.....	.....	606, 0.6	.....
2/20/14	.....	.....	+	0.3, +++	.....	25 40
3/ 5/14	.....	.....	.....	.....	606, 0.6	.....
3/ 6/14	.....	.....	.....	0.4, +++	.....	25 50
3/19/14	.....	.....	.....	.....	606, 0.6	.....
3/20/14	++	.....	.....	0.3, +++	.....	25 50
4/ 6/14	.....	.....	.....	.....	606, 0.6	.....
4/ 7/14†	.....	.....	+	0.3, +++	.....	25 50
2/ 6/15‡	—	.....	.....	0.5, +++	.....	.....
2/15/15	.....	.....	.....	.....	914, 0.9	.....
2/16/15	.....	1	—	0.5, +++	.....	25 50
3/ 2/15	.....	.....	.....	.....	914, 0.9	.....
3/ 3/15	.....	0	—	.....	.....	25 50

* Surer on feet. Walks better.

† No sensory disturbance subjective or objective. Can walk and run.

‡ Also negative when done with two and three times the usual amount of patient's serum.

Results and Present Condition.—The patient is now able to follow his usual occupation without difficulty. April 30, 1915, he wrote that he walked normally, though he felt a little stiffness from his knees down and that he could cover three or four miles a day without difficulty. There has been no change in the physical findings except that practically no sensory disturbances exist. There has been a marked improvement in the serological findings. From a functional and symptomatic point of view this patient is vastly improved.

Case 3.—(Table 3.) H. O. B. Male, aged 34. Single. Cerebrospinal syphilis with very acute onset of symptoms. Had been drinking heavily and was brought to the Cleveland City Hospital for what was presumed to be

TABLE 3.—(Case 3.) Cerebrospinal Syphilis

H. O. B., aged 34. Acute cerebrospinal syphilis. Result: marked improvement, Cleveland City Hospital.

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intravenous Salvarsan gm.	Serum Intraspinously c.c.	pct.
		Cells per c.mm.	Noguchi Globulin Test	Wassermann Reaction No. c.c.			
3/21/14 *	+++	550	++	0.1, +++	.....	.....	
4/13/14 †	.....	155	Faint +	0.1, +++	.....	.....	
4/27/14	.....	.....	.....	.....	0.45	.....	
4/28/14	.....	.....	.....	0.2, +++	.....	25	40
5/ 2/14	+++	.....	.....	.....	.....	.....	
5/12/14	.....	.....	.....	.....	0.6	.....	
5/19/14	.....	.....	.....	.....	0.6	.....	
5/20/14	.....	30	+	0.2, +++	.....	25	40
6/ 2/14	.....	.....	.....	.....	0.6	.....	
6/ 3/14	.....	30	+	0.3, +++	.....	25	40
6/ 5/14	+++	.....	.....	.....	.....	.....	
6/18/14	.....	.....	.....	.....	0.6	.....	
6/19/14	.....	15	+	.....	.....	25	40
7/ 8/14	.....	.....	.....	.....	0.6	.....	
7/ 9/14	.....	10	+	0.3, +++	.....	25	50
7/27/14	.....	.....	.....	.....	0.6	.....	
7/28/14 ‡	.....	5	0	0.3, +++	.....	25	50
8/ 9/14 §	.....	7	0	0.2, +++	.....	.....	
5/31/15 ¶	Negative	3	0	0.5, + 0.1, +++	.....	.....	

* Wild delirium followed by unconsciousness with fever and signs of acute meningeal involvement. Double papillitis.

† Mercury biniodid, ½ gr. intramuscularly, eighteen doses.

‡ Serum followed by very severe reaction. Heavy trace of albumin in urine.

§ Discharged from the hospital with slight facial paresis and paresis of left arm. Much improved.

¶ Only slight slurring of speech and paresis of left arm. No treatment from 8/9/14 to 5/21/15.

delirium tremens. Two weeks after admission the patient developed a paresis of the left arm and of the left side of the face associated with a marked rigidity of the neck and double Kernig's sign and a double Babinski reflex. The pupils reacted to light. The right was larger than the left. The temperature rose to 103.6 and the pulse to 108. He had incontinence of both urine

and feces. The spinal fluid was turbid, showed 550 cells per c.mm., a heavy Noguchi globulin reaction and a positive Wassermann reaction in 0.1 c.c. of the spinal fluid. Under intramuscular injections of mercury biniodid, gr. ½, of which he received eighteen, together with large doses of potassium iodid, the acute symptoms cleared up, but the patient was very weak. His mentality was slow and his speech halting. His first intraspinal injection was given April 28, 1914. During three months following the patient received seven intravenous injections of salvarsan, a total of 4.05 gm., and four intraspinous injections of 25 c.c. of 40 per cent. serum and two intraspinous injections of 25 c.c. of 50 per

TABLE 4.—(Case 4.) Tabes Dorsalis

C. H. Z., aged 44. Tabes dorsalis several years' duration. Syphilis denied. Result: marked improvement.

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intravenous Salvarsan gm.	Serum Intraspinously
		Cells per c.mm.	Noguchi Globulin Test	Wassermann Reaction No. c.c.		c.c. pct.
6/ 4/14	.....	.....	.....	.....	914, 0.6	.....
6/ 5/14	.....	62	++	0.2, +++	.....	25 40
6/18/14	.....	.....	.....	.....	914, 0.9	.....
6/19/14	.....	15	+	0.4, +++	.....	30 40
7/29/14	.....	.....	.....	.....	914, 0.9	.....
8/ 1/14	.....	0	±	0.5, —	.....	30 40
				1.0, +++		
9/ 9/14	.....	.....	.....	.....	914, 0.9	.....
9/10/14	.....	6	—	0.5, —	.....	20 40
				1.0, +++		
10/ 1/14	.....	.....	.....	.....	914, 0.9	.....
10/ 2/14	.....	.....	.....	0.8, +++	.....	20 40
10/30/14 *	.....	.....	.....	.....	606, 0.4	.....
10/31/14	.....	.....	.....	0.8, ++	.....	30 40
				1.0, +++		
12/ 2/14	.....	.....	.....	.....	606, 0.4	.....
12/ 3/14	.....	1	—	0.7, +++	.....	30 40
1/28/15	.....	.....	.....	.....	606, 0.5	.....
1/29/15 †	.....	0	±	0.5, —	.....	15 40
				1.0, +++		
3/18/15	.....	.....	.....	.....	606, 0.5	.....
3/19/15	.....	0	—	1.0, ±	.....	25 40

* Gained in weight. No crises since 10/2.
† No crises. Occasional twinge in leg.

cent. serum. After the last injection the patient had a severe reaction, characterized by pains in the head and abdomen and by albuminuria. While under intraspinal treatment the patient gained 20 pounds in weight. His mentality improved greatly and his general strength increased. He left the hospital and returned to his work as a manager of a shoe store, which he carried out to the satisfaction of his employers. He was seen again nine months after his discharge from the hospital. The patient was well nourished. His speech was slightly halting, but questions were answered intelligently. He showed no tendency to the speech defects typical of paresis. The pupils reacted a little sluggishly to light. The paresis of the left arm was still present but no other abnormalities were made out on physical examination. The blood Wassermann

reaction was negative. The spinal fluid showed three cells per cubic millimeter, a negative Noguchi globulin reaction and the Wassermann reaction gave a strongly positive reaction with 0.7 c.c. of the fluid.

In this case the acuteness of the symptoms at onset is very striking. Under treatment the symptomatic improvement was very marked, while the serological findings in blood and spinal fluid remained almost the same, except for the diminution in cells and globulin content in the spinal fluid.

Results and Present Condition.—Observation after nine months without treatment showed that the patient had returned to economic efficiency and it is interesting to note that during this time his serological improvement had become very marked. His process has not only been arrested but has receded to an apparently harmless degree of latency. He should, of course, receive treatment until all the serological signs of the disease have disappeared.

Summary of Treatment.—This patient received seven intravenous injections (a total of 4.05 gm. salvarsan) and six intraspinal injections preceded by 9 gr. of mercury biniodid intramuscularly, during a period of a little less than five months.

Case 4.—(Table 4.) C. H. Z. Tabes dorsalis (moderately advanced). Man, 44 years old. Had been troubled for some years with gastric crises and with incontinence of urine. No history of a luetic infection could be obtained. The pupils were pin point and did not react to light. Knee and ankle jerks were lacking, muscle sense was impaired and Romberg's sign was present. Received first intraspinous treatment June 5, 1914. After the first combined treatment there was a marked subsidence of pain, and after the third treatment he began to show decided improvement in general condition. The spinal fluid taken after two combined treatments showed a disappearance of the lymphocytosis and with 0.5 c.c. the Wassermann reaction was negative.

Summary of Treatment.—He has received neosalvarsan or salvarsan intravenously nine times (the total being equivalent to 4.6 gm. of salvarsan) and nine serum injections. The reaction to the intraspinous treatments were at first severe but latterly they have been less marked.

Present Condition.—Clinically his present condition is greatly improved. The pains have disappeared, except for recrudescences in mild form when he is fatigued. His weight has increased, he feels well and his economic efficiency has been restored. Physical examination shows no change in pupils or reflexes but the Romberg sign is less marked and the muscle sense is improved. The laboratory findings are very gratifying. The cell count is normal, globulin is absent, and even when 1.0 c.c. of spinal fluid was employed the result of the Wassermann reaction was negative (±).

Case 5.—(Table 6.) Mrs. W. A. D. Early tabes. Female, 34 years of age. Married. Complained of occasional incontinence of urine and stumbling. The symptoms had been in evidence for one and one-half years. Infection had taken place twelve or thirteen years previously. At that time she had received "pills" for a year only. Examination showed inequality of pupils with failure to react to light, absence of knee and ankle jerks and Romberg's sign. For a year before consulting us some soluble mercurial preparation had been administered intensively. Under this therapy she made some improvement, but it was slight and very slow. The Wassermann reaction, using blood serum, was strongly positive and the spinal fluid showed 95 cells per c.mm. a positive globulin test, a Wassermann reaction when only 0.1 c.c. was employed.

The improvement in this case after the institution of intravenous and intraspinous treatment was rapid and striking. After the first two treatments she reported that she was able to run up stairs from the basement to the second story, while previously in ascending stairs she had to stop after climbing

up a few steps "to take the twist out of her legs." The subarachnoid fluid showed the Wassermann reaction to be less than one-fifth as strong as it had been. Altogether this patient has been under observation six months.

Summary of Treatment.—The patient has taken six injections of neosalvarsan or salvarsan (the total being equivalent to 3.0 gm. of salvarsan) and has been given two intraspinous injections.

Present Condition.—When the spinal fluid was examined last the lymphocytosis and the trace of globulin had disappeared, and the Wassermann reaction was negative with 0.5 c.c., though positive with 1.0 c.c. In addition, the clinical result in this case has been very striking. The incontinence has cleared up, the gait has improved. She is much stronger and can accomplish more. The pupillary reaction and the ankle and knee jerks are unchanged.

TABLE 5.—(Case 5.) Tabes Dorsalis

Mrs. W. A. D., aged 34. Early tabes dorsalis. Syphilis admitted. Result: marked improvement.

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intravenous Salvarsan gm.	Serum Intraspinously c.c. pct.
		Cells per c.mm.	Noguchi Globulin Test	Wassermann Reaction No. c.c.		
10/14/14	+++	.....	.....	.....	.....	.....
10/19/14	.....	.....	.....	.....	914, 0.6	.....
10/20/14	.....	95	+	0.1, +++	.....	25 40
11/13/14 *	.....	.....	.....	.....	914, 0.9	.....
12/30/14	.....	.....	.....	.....	914, 0.9	.....
12/31/14 †	.....	.....	.....	0.5, +	.....	21 50
				0.1, +++	914, 0.9	.....
1/22/15	.....	.....	.....	.....		
2/ 5/15	.....	.....	.....	.....	606, 0.4	.....
3/ 5/15	‡—	.....	.....	.....	606, 0.4	.....
4/ 8/15	.....	1	—	0.5, —	.....	.....
				1.0, +++		

* Already feels much better.

† Coordination much improved.

‡ Also negative when reaction was performed using two and three times usual amount of patient's serum.

Case 6.—(Table 6.) D. W. H. Moderately advanced tabes. Man, aged 39. He acquired syphilis in 1901. His treatment was interrupted after six months on account of very severe typhoid fever which intervened. Following convalescence from typhoid, iodid and mercury were taken by mouth periodically, and since then he has had broken courses of mercury. The first symptoms of nervous disturbance came in March, 1913. After this he had a nervous break down associated with dyspepsia. In October, 1914, he noted stiffness and numbness in the extremities. Soon after he had severe pain in the back and had much difficulty with locomotion on account of "stiffness in his legs."

The patient has received a portion of his treatment from Dr. H. M. Brundage of Columbus, who has very courteously furnished us with a synopsis of his findings. When the patient was first seen by him Dec. 28, 1914, the blood serum Wassermann reaction was negative and the spinal fluid showed 150 cells

per cubic millimeter, a decided trace of globulin and a strongly positive Wassermann reaction, the quantities varying from 0.1 to 0.5 c.c. (expressed in terms of modified technic). Dr. Brundage administered a total of three intravenous and three intraspinous injections. The patient noted decided improvement three days after his first treatment.

When we saw the patient the pupils showed inequality but reacted promptly to light and accommodation. The knee jerks and ankle jerks were absent. Muscle sense was impaired. There were marked sensory changes. A slight Romberg sign was present and the patient had a typical tabetic gait. The spinal fluid showed that the cell count had diminished to 2 per cubic centimeter, the butyric acid reaction was only faintly positive and the Wassermann reaction was negative with 0.5 c.c., but strongly positive with 1.0 c.c.

TABLE 6.—(Case 6.) Moderately Advanced Tabes

D. W. H., aged 39. Moderately advanced tabes. Result: marked improvement.

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intravenous Salvarsan gm.	Serum Intraspinously c.c. pct.
		Cells per c.mm.	Noguchi Globulin Test	Wassermann Reaction No. c.c.		
Previous to March, 1915*	—	150	+++	0.2, +++	†	‡
3/13/15	—	.....	.....	.....	.....	.....
4/ 9/15	.....	.....	.....	.....	0.4	.....
4/10/15	.....	2	Faint +	0.5, — 1.0, +++	.....	30 40
5/ 7/15	.....	.....	.....	.....	0.4	.....
5/ 8/15	.....	0	—	0.5, — 1.0, +++	.....	30 50
6/11/15	.....	.....	.....	.....	0.4	.....
6/12/15	.....	.....	.....	0.7, — 0.9, + 1.0, +++	.....	28 50
7/30/15	.....	.....	.....	.....	0.5	.....
7/31/15	—	1	Faint +	0.5, — 1.0, ±	.....	32 50

* While he was under the care of Dr. W. H. Brundage of Columbus, Ohio, to whom we are indebted for the above data.

† Three injections of 0.6 gm. followed by three intraspinal treatments of 20 c.c. of 50 per cent. serum-NaCl mixture.

‡ Marked clinical improvement.

Summary of Treatment.—He has received in all seven intravenous injections of salvarsan, a total of 3.5 gm., and seven intraspinal injections of salvarsanized serum.

Present Condition.—At present the appreciation of pain has returned in both legs, muscle sense is accurate and the vibratory sense has returned over the greater part of both legs. The patient has no pains and no stiffness, he takes exercise and goes about his business with zest and is living a normally efficient existence. The Wassermann reaction is negative in the blood. The globulin content of the spinal fluid is not increased. There is one cell to the cubic millimeter and the Wassermann reaction on the spinal fluid is but a plus-minus reaction when 1.0 c.c. of the spinal fluid is used. This case can fairly be considered at present a clinical and serological cure.

Case 7.—(Table 7.) H. R. Moderately advanced tabes. Male, aged 32. Married. First intraspinal treatment given April 23, 1914. Patient was infected eleven years ago. There were no noticeable secondary manifestations so that no treatment was taken until two years after the infection, when sores appeared in the mouth and throat. For five years the patient had suffered excruciating, lancinating pains in the legs. The crises of pain sometimes lasted for thirty-six hours. There was occasionally involuntary micturition. The patient was a well developed young man. The pupils were widely dilated and reacted to light. The knee and ankle jerks were absent. There was a slight Romberg's

TABLE 7.—(Case 7.) Moderately Advanced Tabes

H. R., aged 32. Moderately advanced tabes. Duration: five years. Syphilis admitted. Result: improvement.

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intravenous Salvarsan gm.	Serum Intraspinously c.c.	pct.
		Cells per c.mm.	Noguchi Globulin Test	Wassermann Reaction No. c.c.			
3/28/14	+++*	.....	.....	.....	.....	.....	
4/22/14	.....	.....	.....	.....	914, 0.9	.....	
4/23/14	.....	10	++	0.4, — 0.5, +++	.....	25	40†
5/27/14	.....	.....	.....	.....	606, 0.4‡	.....	
5/28/14	.....	0	.....	0.5, — 1.0, +++	.....	25	40
6/17/14	.....	.....	.....	.....	606, 0.4	.....	
6/18/14	.....	3	+	0.5, — 1.0, +++	.....	25	40
7/22/14	.....	.....	.....	.....	606, 0.45§	.....	
7/23/14	.....	.....	.....	0.5, — 1.0, +++	.....	20	40
9/ 3/14	.....	.....	.....	.....	606, 0.4	.....	
9/ 5/14	+++	0	+	0.5, — 1.0, +++	.....	20	50¶
1/ 6/15	.....	.....	.....	.....	914, 0.6	.....	
1/ 7/15	.....	.....	.....	1.0, —	.....	25	40

*This reaction was so strong that it was given with one-eighth the usual amount of the patient's serum.
† Very severe reaction.
‡ Leg pains worse.
§ Feels wonderfully well, little pain.
¶ Pains have returned. Not so severe.

sign. The blood showed a strongly positive Wassermann reaction. The spinal fluid showed a marked increase in the globulin content, 10 cells to the cubic millimeter, and a Wassermann reaction positive with 0.5 c.c. of the fluid.

Summary of Treatment.—This patient was under our observation for ten months, during which time he received six intravenous injections of salvarsan or neosalvarsan (a total equivalent to 2.65 gm. of salvarsan) and six intraspinous injections. In addition to this he received intramuscular injections of mercury salicylate with regularity.

Results and Present Condition.—Symptomatically the patient showed improvement in that the lightning pains abated temporarily. Later they became trouble-

some again. The spinal fluid findings are interesting in that after five intraspinal injections they disappeared entirely, although the blood still remained positive. His last combined treatment was in January, 1915. In April, 1915, he wrote us the following: "I have the pains some, but less severe. My head is clear. I go sometimes a week without a sign of a pain . . . sleep well, which certainly goes to show that either one of the treatments" [intraspinal or mercury] "or the combination of the two has not been without result." In July, 1915, seven months after his last treatment, we are informed that the patient died of an acute nephritis following a severe, widespread ivy poisoning.

Case 8.—(Table 8.) L. B. D. Advanced tabes. Male, aged 40. Married. First intraspinal treatment Nov. 11, 1914. Infected with syphilis twelve years previously. There were no secondary manifestations, so that nothing but local treatment was ever given. The spinal cord symptoms had been present for a

TABLE 8.—(Case 8.) Advanced Tabes

L. B. D., aged 40. Advanced tabes dorsalis. Symptoms of several years' duration. Syphilis admitted. Result: slight improvement.

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intravenous Salvarsan gm.	Serum intraspinously
		Cells per c.mm.	Noguchi Globulin Test	Wassermann Reaction in c.c. Sp. Fluid		c.c. pct.
8/26/14	+++	.....	.....	.....	.....	.....
11/10/14	.....	.....	.....	.....	914, 0.6	.....
11/11/14	.....	23	++	0.3, +++	.....	20 40
12/ 1/14	.....	.....	.....	.....	914, 0.8	.....
12/ 2/14	.....	2	+	0.2, +++	.....	25 40
12/18/14	.....	.....	.....	.....	914, 0.9	.....
12/19/14	.....	1	+	0.3, ++ 0.4, +++	.....	25 50*
1/ 4/15	.....	.....	.....	.....	606, 0.4	.....
1/ 7/15	.....	1.3	++	0.2, + 0.3, +++	.....	22 50

* Walks better.

number of years. He had lost much weight. His color was yellowish. He was distinctly emaciated and anemic. The pupils were unequal in size and did not react to light. The knee and ankle jerks were exaggerated. There was a marked ataxia. The blood showed a strongly positive Wassermann reaction. The spinal fluid showed a marked increase in globulin, 23 cells per cubic millimeter, and a Wassermann reaction which was positive when 0.3 c.c. of the fluid was used. We were inclined to expect little, if any, improvement in this case in the light of the low cell count combined with the symptoms of rapid degeneration.

Summary of Treatment.—He received four intravenous injections of salvarsan or neosalvarsan (a total equivalent of 1.92 gm. of salvarsan) in a period of two months. This was preceded by two months of intensive mercurial injections.

Results and Present Condition.—The present condition is unchanged. The cell count in the spinal fluid fell from 23 to 1.3 per cubic millimeter, while the globulin content and the Wassermann reaction showed no diminution.

Case 9.—(Table 9.) A. J. K. Moderately advanced tabes. Male, aged 31. We had seen this patient in consultation in November, 1911. At that time he gave a history of having been infected six years previously and of "taking pills" for three years, almost constantly. He then had a sensation of a band around the waist and numbness in the hands and feet. Even at that time signs of moderately advanced tabes were definite and unmistakable. The blood Wassermann reaction was strongly positive. On account of the then prevalent distrust of salvarsan in neurological conditions, vigorous mercurial treatment was employed exclusively. With this he grew rapidly worse and had a partial paraplegia. When seen again in January, 1914, he had been having daily mercury injections for six months and a dose of neosalvarsan intramuscularly. He was up and about and felt fairly well. The blood Wassermann reaction was

TABLE 9.—(Case 9.) Moderately Advanced Tabes

A. J. K., aged 31. Moderately advanced tabes dorsalis. Duration: over three years. Syphilis admitted. Result: slight improvement.

Date	Wasser-mann Reaction Blood	Cerebrospinal Fluid			Intra-venous Salvarsan gm.	Serum Intra-spinously	
		Cells per c.mm.	Noguchi Globulin Test	Wasser-mann Reaction in c.c. Sp. Fluid		c.c.	pct.
11/25/11	+++	.....	.....	.....	.....	.....	
1/17/14	+	.....	.....	.....	.....	.....	
11/28/14	+*	.....	.....	.....	.....	.....	
12/ 3/14	.....	.....	.....	.....	914, 0.9	.....	
12/ 4/14	.....	12.5	+++	0.2, +++	.....	25	40
12/29/14	.....	.....	.....	.....	914, 0.9	.....	
12/30/14	.....	.....	+++	0.2, +++	.....	21	50
2/ 5/15	.....	.....	.....	.....	606, 0.5	.....	
2/ 6/15	.....	1.3	+++	0.2, + 0.3, +++	.....	25	50
3/19/15	.....	.....	.....	.....	606, 0.4	.....	
3/20/15	.....	0	++	0.2, — 0.3, +++	.....	30	40
5/29/15	.....	.....	.....	.....	606, 0.4	.....	
5/30/15	.....	0	Not examined	0.2, + 0.3, +++	.....	30	50

* Reaction +++ when twice usual amount of patient's serum was used.

very faintly positive. We began the Swift-Ellis treatment in December, 1914. Then the pupils were small and showed no light reaction, the knee and ankle responses were abolished and there was a slight Romberg sign. Mentally the patient seemed rather slow. The spinal fluid findings were: cell count, 12.5; globulin, very heavy trace; Wassermann reaction, strongly positive with 0.2 c.c. The Lange colloidal gold test was positive.

Summary of Treatment.—This patient has been under our immediate supervision for only six months. He has had five intravenous injections, two of neosalvarsan and three of salvarsan (the total being equivalent to 2.5 gm. of salvarsan), and four serum injections.

Present Condition.—We feel that he has been under observation too short a time to permit drawing any conclusions of especial value. The spinal fluid lymphocytosis disappeared rapidly, and the patient reports that he feels stronger

and better and that he is able to do more work on his farm this summer than he could a year ago. The history, with the long duration of the condition, the severity of the symptoms, and the extent of involvement, pointed in advance to the need for prolonged treatment.

Case 10.—(Table 10.) J. L. S. General paresis. Male, aged 45. Married. Infected with syphilis twenty years ago. Has taken small amounts of mercury at intervals. Two years ago the patient began to have stomach trouble. He was seen in March, 1915. His speech was thick and he had the classical symptoms of an early paresis. The pupils were irregular and unequal in size. The knee and ankle jerks were exaggerated. There were no definite sensory changes. The blood showed a strongly positive Wassermann reaction. The spinal fluid showed a cell count of 25, a very marked globulin increase and a Wassermann reaction positive in 0.2 c.c. of spinal fluid. The patient had lost much weight

TABLE 10.—(Case 10.) Early Paresis

J. L. S., aged 45. Married. Early paresis. Result: improvement, especially in serological findings.

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intravenous Salvarsan gm.	Serum Intraspinously	
		Cells per c.mm.	Noguchi Globulin Test	Wassermann Reaction No. c.c.		c.c.	pct.
3/20/15	+++	25	++	0.2, +++			
4/23/15					0.35 *		
5/21/15					0.4		
6/10/15					0.4		
6/25/15					0.45		
6/26/15				0.3, — 0.4, +++		20	40†
7/12/15					0.5		
7/13/15		0	++	0.5, — 1.0, +++		28	50‡

* Between 3/20 and 4/23 intensive mercury treatment. No improvement.
† Lange colloidal gold test typical paretic curve.
‡ Lange much less marked.

and was running down rapidly. Between April, 1915, and July, 1915, he has received five intravenous injections of salvarsan (a total of 2.1 gm.) and two intraspinal treatments, one of 40 per cent. and one of 50 per cent. serum. After the first three intravenous injections the patient showed very little change in his condition. In fact, his difficulty in speaking and writing became worse. The spinal fluid withdrawn after the three intravenous injections showed very little improvement. Immediately after the first intraspinal treatment the patient was mentally much worse. He slurred in his speech pitifully and was almost incapable of looking after himself. This condition cleared up and about two weeks later the speech was distinctly clearer. The patient concentrated better. A spinal fluid examined at this time (July 13, 1915) showed no cells, a positive globulin, a Wassermann reaction negative in 0.5 c.c. of spinal fluid, but positive in 1.0 c.c.

While this patient has been under observation too short a time to warrant any conclusions being drawn from the case the changes in the spinal fluid two weeks after the first intraspinal treatment are of considerable interest.

We have given fifty-nine intraspinal injections of autosalvarsanized serum in ten cases. Further, we have given fourteen similar treatments not included in the above series, making a total of seventy-three injections. Following these injections we have seen no symptoms, temporary or permanent, which could in any way be attributed to injury to the central nervous system. We have seen no deaths, paralysis or bladder disturbances. One of our patients died of an intercurrent condition seven months after the cessation of treatment. Two of the patients have experienced no discomfort from the procedure. When gastric crises or lancinating pains exist, we have learned to expect attacks of pain, in all ways similar to the pre-existing crises. These crises usually follow the treatment after an interval of from two to four hours and they are often very severe. Their duration is usually short, and they are followed by much increased periods of freedom from pain. As the treatment continues these postoperative attacks become less and the spontaneous crises often disappear entirely.

It is of interest to note that those patients who have had these reactions of pain following the treatment have showed greater and more rapid improvement than those who had no discomfort from the procedure.

We have found that the increased globulin content in the spinal fluid is very resistant to treatment. A moderate increase in globulin often persists after several treatments, as in Cases 8 and 9, where only a very slight decrease in globulin has occurred after three treatments. The pleocytosis disappears rapidly. In Case 1 lymphocytosis of 550 per cubic millimeter came within normal limits after six intravenous and four intraspinal injections. Cell counts of 150 or below usually diminish to normal limits after from one to three treatments. We have found that the Wassermann reaction in the spinal fluid is the most obdurate of the laboratory findings. The reaction often persists in the larger doses of spinal fluid, long after the other laboratory findings have come within the normal limits.

The changes in the physical findings which we have noted under the intraspinal treatment have been a partial or complete disappearance of disturbances of sensation, lessening or disappearance of ataxia and a marked increase in weight and strength. In no case, so far observed, have we seen absent deep reflexes return, nor have we seen any change in the pupillary reactions.

The abatement or disappearance of symptoms has been most striking. In every instance in which lancinating pains were present, they have either disappeared completely or have diminished so much that they have ceased to be a real annoyance. In Case 3, gastric crises which had nearly incapacitated the patient, have disappeared. Very

striking is the rapid improvement in the general condition, in weight, in strength and in return of the ability to carry on the daily routine of employment; in other words, the practical ending of invalidism. In some cases this improvement in the general condition can be attributed to the abolition of pain, but in others (notably Cases 3, 5 and 9) in which pain had not been a feature, this general betterment was noted. Vesical incontinence in one case has been so much less frequent that it has almost ceased to be an annoyance.

RESULTS

The results in six of these ten cases has been a symptomatic improvement so emphatic that the patient's economic efficiency has been restored. They are able to work and to enjoy life to all intents and purposes as normal individuals.

We feel that the best results will be obtained in cerebrospinal lues, and in tabes of the early or moderately advanced types. In far advanced tabes the results are in most cases dubious to say the least. Our own experience with paresis is so limited that we should have no right to make any generalization. It seems probable to us, however, that very little can be done to improve permanently a paresis once it is well established.

In concluding we feel that we can state fairly that the Swift-Ellis method is safe when the original technic is followed out to the letter. The claim of the originators that it is a valuable adjunct to the treatment of syphilitic involvement of the central nervous system is sustained as far as tabes dorsalis and cerebrospinal syphilis are concerned. It is a method which is not essential in all cases, but which applied carefully and controlled intelligently will bring about definite amelioration in symptoms and in laboratory signs where other accepted modes of attack have failed.

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PROTHROMBIN AND ANTITHROMBIN FACTORS IN THE COAGULATION OF BLOOD *

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Few have studied the prothrombin and antithrombin factors of coagulation of the blood in human cases. Howell[1] devised methods to study these factors and has reported a deficiency of prothrombin in hemophilia with relative excess of antithrombin, a diminution of antithrombin in cases of spontaneous thrombosis and no abnormality in the cases of purpura he studied.

Whipple[2] reported increased amounts of antithrombin and a prothrombin deficiency in hemorrhagic cases, but his results are to be criticized in that he did not take into consideration normal variations, and that dog blood was used to control human. Austin and Pepper[3] have made studies on the coagulation of oxalated plasma. In one case of purpura they found delayed coagulation on recalcification in the presence of thromboplastic solutions and attributed it to increased antithrombin. Since our work was begun, Hess,[4] using Howell's methods, has published the results of a study of these factors in scurvy, which were negative.

Whipple and Moss[5] have pointed out that a knowledge of how these factors may vary in hemorrhagic disease is important in considering treatment, for on theoretical grounds one would not treat a case of bleeding due to an increased amount of antithrombin the same as one due to a deficiency of prothrombin.

In certain cases perhaps one might be able to predict when thrombosis was apt to take place by a fall in the amount of antithrombin and be able to give something to prevent thrombus formation.

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1. Howell: THE ARCHIVES INT. MED., 1914, xiii, 76.
2. Whipple: THE ARCHIVES INT. MED., 1913, xii, 637.
3. Austin and Pepper: THE ARCHIVES INT. MED., 1913, xi, 305.
4. Hess: AM. JOUR. DIS. CHILD., 1914, viii, 386.
5. Whipple and Moss: Forchheimer's Therapeutics of Internal Diseases, 1914, v. 801. D. Appleton & Co.

With Dr. Howell's and Dr. Thayer's stimulating interest and help a further study of the blood in various diseases, with reference especially to the content in antithrombin and prothombin, has been made; with the hope that we could say definitely that there are bleeding cases due to increased amounts of antithrombin and others due to diminished amounts of prothrombin, and that diminished amounts of antithrombin occur only in cases that are subject to or have thrombosis. A consideration of these tests, the normal variations of the factors, and the findings in various pathologic conditions form the basis of this paper.

METHOD OF OBTAINING BLOOD

Specimens of blood were drawn by venepuncture into an all-glass graduated syringe, previously sterilized and rinsed with normal salt solution, from which a measured amount was put into a tube with a measured amount of 1 per cent. sodium oxalate in 0.9 per cent. salt solution. Usually 5 c.c. of blood were mixed with 0.7 c.c. of the oxalate solution. However, the series of plasmas tested at any one time were diluted the same.

Precaution was taken that the venepuncture was done cleanly, so that the needle was not scraped about in the tissue, thus covering it with the tissue juice (thromboplastic material). Care was taken to get no air bubbles in the syringe as the blood was drawn, though in some instances where this occurred, no very definite differences in the prothrombin or antithrombin were noted. If any hemolysis had taken place in the plasma, as from traces of water left in the syringe or other cause, it was rendered valueless for prothrombin and antithrombin determinations because of liberated thromboplastic material.

Each specimen being mixed with the oxalate solution was brought to the laboratory and centrifuged at high speed, about 3,000 revolutions a minute, for just twenty minutes. The plasma was then pipetted off from the cellular elements and examined for prothrombin and antithrombin.

PROTHROMBIN

(*A*). *Method of Testing.*—To test the relative amount or efficiency of prothrombin, the method of recalcifying the oxalated plasma as described by Howell,[1] was used. The method employed is as follows:

Five drops of the plasma were placed in five tubes (1.3 cm. diameter, 6.8 cm. high with flat bottom) and to these were added in series 1, 2, 3, 4, and 5 drops of a calcium chlorid solution. The time, called the prothrombin time, that it took the first clot to form which was not dislodged on inversion of the tube, was taken to represent the prothrombin; that is, the clotting time with the optimum amount

of calcium. It was rare not to find at least two tubes clotting in practically the same time, not infrequently four of the five tubes would clot within a minute of each other. If the minimum was long, twelve to fourteen minutes, then it was more usual to see a well-marked graded difference in the clotting (i. e., for example, the 5-drop tube clotted in 24 minutes, the 4-drop in 18, the 3 in 14, and the 2 in 12 minutes) than if six to eight minutes was the minimum time. Perhaps this was because a proportional difference was less easily detected in the shorter period of time.

After the calcium chlorid was added, the tubes were immediately shaken to mix it with the plasma. Care was taken that the tubes were not jarred when the clotting was going on; they were, however, gently tilted, equally in the different specimens, to see if clotting had taken place. The test was always made within two hours after the collection of the blood and usually within an hour. Allowing the plasma to stand some hours before the test is made will usually not only vary the prothrombin time, but often the amount of calcium necessary to obtain it. Very slight changes may occur in the prothrombin time of a plasma which has stood two or three hours. The test was made at room temperature, which though not taken, we believe was always about 70 F.

It has been shown by Lee and Vincent,[6] among others, that a plasma in which the platelets are kept as nearly as possible intact by using greased cannulas and drawing the blood directly into oxalate, will vary the platelet content of the plasma and in turn vary the prothrombin time, being longer the fewer the platelets. We found in three instances, that a difference of centrifuging fifteen or thirty-five minutes plasma collected by our methods made no appreciable difference in the prothrombin time, or in the amount of calcium needed for this time.

Two calcium chlorid solutions were used during our study, one made from fused calcium chlorid, the other of pure recrystallized calcium chlorid, containing water of crystallization. The latter when compared with the former usually caused a given plasma to clot in the same time, though sometimes it caused a clot to form a half minute sooner.

It is advisable to use for this test a solution of the calcium chlorid containing water of crystallization; for numerous solutions were made from different stocks and those made from deliquescent calcium chlorid always acted the same. Those from fused calcium chlorid often caused a delay, even as much as four minutes in the prothrombin

6. Lee and Vincent: The Archives Int. Med., 1914, xiii, 398.

time, and the difference between the clotting times of a plasma with different amounts of calcium was distinctly greater than when the solutions of deliquescent calcium chlorid were used. This is perhaps because the fused calcium chlorid contained something that interfered with clotting.

The optimum amount of calcium was always essentially the same unless the contrary is stated, provided the dilution of the blood with oxalate solution was the same. Though the amount of oxalate used to dilute a given blood may vary, the prothrombin time is the same within a minute.

(*B*). *Normal Prothrombin.*—Ninety-one determinations of prothrombin time, which varied from six to fourteen minutes, averaging nine and one-half, were made from sixty-six normal persons between April, 1914, and March, 1915. In comparing two prothrombin times, the longer time was taken to represent a less amount of prothrombin or a relative deficiency of prothrombin; the shorter the reverse.

During the time these normals were tested, seventy-three cases with various diagnoses were studied whose prothrombin time (eighty-nine determinations) was found to be between six and fourteen minutes. The accompanying table (Table 1) shows the frequency of the varying normal prothrombin times.

TABLE 1.—Showing Normal Variations of Prothrombin Time

	Minutes				
Prothrombin time*	6	8	10	12	14
Determinations on normal persons	14	27	27	19	4
Determinations on diseased persons	17	28	25	12	8

* Clots only recorded on even minutes.

During warm weather the prothrombin time was usually shorter than in cold weather. Studies now being made tend to show that the temperature at which the test is made, and at which the plasma is kept before the test is made, will vary the prothrombin time, so that for accuracy the test should be run at the same temperature, preferably 21 C.

There was a distinct tendency for the cases of a given day to be grouped in a high, medium or low range; that is, one would see on a different day variations of 10 to 14, 6 to 8 or 10, or 8 to 12; that is, not over 4 minutes difference. However, there are three instances among the diseased and but one instance among the normals in which 6 and 14 occurred at the same time.

One cannot say from the cases studied by the methods used that either six minutes or fourteen minutes is abnormal for prothrombin time, though the observer on different occasions may have the impression that six or fourteen in certain instances is abnormal.

What effect diet, exercise, time of day, acidity of the blood, etc., may have on this reaction has not yet been determined.

A delayed prothrombin time, spoken of as a low prothrombin, may be dependent on the antithrombin content of the plasma. One must realize that this test for prothrombin is a relative test of efficiency, because in an oxalated plasma we have not only prothrombin but antithrombin, fibrinogen and thromboplastin. If there is a high antithrombin content, the clotting on recalcification would perhaps be somewhat delayed provided the prothrombin were not increased. It might, with the same high antithrombin content, be still more delayed if the prothrombin were diminished, but if the antithrombin were normal or less than normal and there was a delayed prothrombin time, one could say the prothrombin was the lacking element. Addis[7] has suggested that the delayed prothrombin time occurring in hemophilia is not due to a diminished amount of prothrombin but to an alteration that makes it slowly available for use. This may be true of any delayed prothrombin time, there being no way to determine the actual amount of prothrombin. The amount of fibrinogen in human cases is probably always enough to give a clot within the normal time, though its firmness may be changed.

A certain amount of thromboplastin is normally present in plasma in the form of disintegrated blood plates, etc. A marked lessening of this element could probably cause a delayed prothrombin time.

ANTITHROMBIN

(*A*). *Method of Testing.*—The antithrombin was tested for in the same specimen of blood as the prothrombin, usually two to three, sometimes as many as six hours after the blood was drawn.

A method for testing antithrombin with which we have had as yet little experience has recently been described by Hess,[8] in which antithrombin from the cases to be tested is added to an oxalated plasma and the times of clotting on recalcification with the optimum amount of calcium, compared. Whipple, among others, tested for antithrombin by the amount of thromboplastic material required to neutralize the antithrombin.

The test we used is of the type described by Howell.[1] All the plasmas in which antithrombin was to be determined were slowly heated simultaneously on a water bath to 60 C., thus destroying the prothrombin and precipitating the fibrinogen. These were filtered, the filtrate containing only antithrombin as far as elements of coagulation are concerned.

7. Addis: Jour. Path. and Bact., 1911, xv, 427.
8. Hess: Jour. Exper. Med., 1915, xxi, 338.

For each antithrombin test a series of tubes was set up with one drop of antithrombin in each tube, to which was added a varying number of drops of antithrombin, usually 2, 3, 4 and 5 drops, and then these two substances were allowed to remain in contact for a given period of time, usually fifteen minutes. It is important that the tubes be twisted so that few drops of thrombin and antithrombin get well mixed and this should be done at once after the two substances are in the tubes so that the clots to be compared have the thrombin and antithrombin in contact an equal length of time. After the given interval had elapsed the same amount of a fibrinogen solution (usually 10 drops) was added to each tube. The tubes were then shaken to mix the materials and frequently looked at to see when the first clot appeared. Those tubes containing the least antithrombin would clot first, and those with the greatest, last.

Thrombin was prepared according to Howell's[9] method and kept in watch crystals. To obtain a solution of thrombin it was only necessary to dissolve the contents of a watch crystal in distilled water, the amount varying with the strength of the thrombin. Later observations showed that thrombin made by carrying the process through only to the stage of dialysis, though not entirely purified from other protein substances, was free from other elements of coagulation and yielded a satisfactory and stronger solution. It should be used unfiltered, as filtering weakens it.

For fibrinogen, dried oxalated cat's plasma made according to Howell's method was usually used. This was kept in watch crystals, redissolved in normal salt solution and filtered.

(*B*). *Consideration of an End Point.*—Difficulty was found in obtaining a fibrinogen plasma which would give a good firm clot with thrombin in about three minutes, and which would give a similar clot in the presence of antithrombin in a period of time of over ten minutes; an amount of time found necessary to distinguish differences readily. Dried plasmas would not act always in the same manner. Some of the difference seemed to be due to the individual animal.

A given antithrombin, thrombin and fibrinogen mixture that clots if undisturbed in ten minutes as a solid jelly (i. e., with a period of but a minute when it is in a half jellied condition) if shaken frequently, causes a lumpy or perhaps sliding jelly-like clot to form in very closely the same time, which, if then left undisturbed, will become a solid jelly in perhaps fourteen to twenty minutes or even longer. If the same combination is shaken more violently, often flocculi will appear in

9. Howell: Am. Jour. Physiol., 1910, xxvi, 453; ibid., 1913, xxxii, 264

about the same time as the solid jelly did in the first instance, but to reach the solid jelly stage will then usually take much longer.

Several series of antithrombin determinations were made on the same specimens with different fibrinogen solutions. Some gave flocculi, others a firm jelly and some a sliding jelly or lumpy clot. The comparisons between the different specimens were very similar, provided one read for the end-point the time when a clot of any sort first appeared. A solid clot made a neater and more easily distinguishable end-point. Flocculi were easier to read than sliding jelly or lumpy clots. If a shriveled-up, veil-like clot occurred it was impossible to tell when it first appeared.

Using the same solutions, slight differences in the amount of antithrombin may cause differences in the type of initial clot.

If flocculi are to be read as an end-point, the tubes must be examined and shaken frequently to break up these small white particles easily adhering to the glass. On the contrary, to obtain a solid jelly end-point, the tubes must be disturbed as little as possible. All tubes between which comparisons are to be drawn must be tilted or shaken equally.

(*C*). *Choice of Fibrinogen Solution.*—Difficulty in getting a series of tubes to clot as solid jellies led to attempting the use of different fibrinogen solutions.

A dried, clear cat's plasma was made by a method suggested by Dr. Howell, similar to the previous one he described, but dialyzing the plasma against 0.7 per cent. NaCl with 0.05 per cent. KH_2PO_4 for one hour, changing the solution at the end of half an hour, instead of a twelve-hour dialysis against 0.9 per cent. salt solution. This method usually yielded a better fibrinogen solution than the older method, but still was often unsatisfactory. Weaker fibrinogen plasma was obtained from dogs.

Fluorid, magnesium sulphate and undialyzed oxalated plasmas dried and redissolved were unsatisfactory.

Solutions of pure fibrinogen prepared according to a modification of Hammarsten's method [precipitation of an oxalated plasma with saturated NaCl solution, centrifuging the precipitate and then washing with half saturated NaCl solution and redissolving in 2 per cent. NaCl (adding a few drops of 1 per cent. solution of sodium bicarbonate to aid solution, if necessary) and repeated once or twice] gave the best material because it allowed a solid jelly clot to form in the presence of strong antithrombin in a period of time permitting one to distinguish a real difference between two specimens. The difficulty with such a solution is that it cannot be kept for use for much more than six days.

One precipitation with the saturated sodium chlorid yielded a fibrinogen solution suitable for this test. Alkali weakens the effectiveness of the fibrinogen.

(*D*). *The Desirable Time to Have Clots Form.*—Thrombin and fibrinogen react quantitatively, as is shown by the curve in the chart (taken from an average of several tests). This chart shows the effect of antithrombin on clotting when previously allowed to stand for a definite period in contact with thrombin. The less thrombin there is in proportion to the antithrombin the greater the time for the clot to form.

Besides changing the amount of thrombin to lengthen or shorten the time the clot appears, one can do so by lengthening or shortening

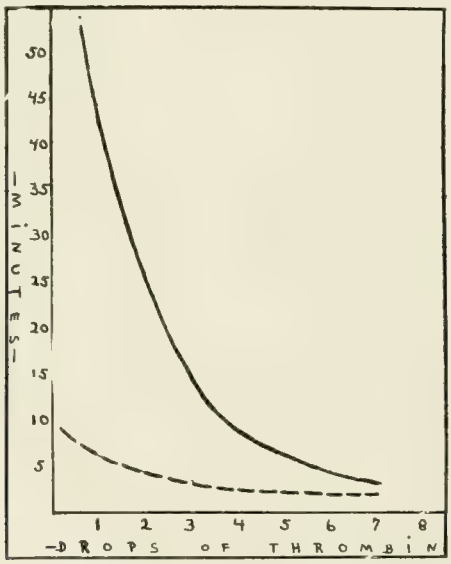

Chart showing that thrombin and fibrinogen react quantitatively. Solid line = thrombin + antithrombin + fibrinogen. Broken line = thrombin + fibrinogen.

the interval that the thrombin and antithrombin remain in contact. This may also change the type of clot.

The materials were always used in such amounts as to cause the first clot to appear in between eight to twenty minutes. If clotting took place rapidly it was difficult to distinguish differences between specimens, if too slowly the end point was difficult to determine.

(*E*). *Use of Antithrombin Factor in Comparison of Cases.*—To compare the antithrombin of a series of specimens determined at the same time with the same solutions, time alone is sufficient, but to com-

pare antithrombin from different cases determined at different times with different solutions, the time in which the clot appears is unsatisfactory.

None of the materials used are stable; temperature varies their action; all lose power on standing. Individual watch crystals of thrombin and fibrinogen plasma made from the same stock vary slightly, the difference depending very likely on the speed with which they were dried.

Heating plasma to 60 C., if done rapidly or slowly, will change somewhat the amount of antithrombin. The amount will also vary if the plasma is heated to 59 or 61 C.

If specimens are collected within about an hour of each other, heated simultaneously and tested at the same time with the same amounts of solutions, their antithrombin content will bear a fairly constant relationship to each other, often varying a little. The relationship if 1 to 1 might become as much as 0.86 to 1 or 1 to 1.15 when repeated tests are made. Such variation is probably due to technic, size of drops, the amount of mixing of thrombin and antithrombin, etc.

The relationships of two specimens will be maintained for at least six hours. Specimens of antithrombin kept on the ice for eighteen hours showed usually the same relationship to each other as when first tested. Though it was evident from the clotting time that antithrombin on standing loses power.

In view of the fact that the relation between a series of specimens keeps constant for hours, and time seems an unsatisfactory way to express antithrombin, the following scheme was devised to allow cases tested at different times to be compared.

A normal control was run with all the cases studied, often two controls, sometimes more. The added time of the specimens from the case clotting between eight and twenty-five minutes was divided by the similar figure for the control and this factor used to express the amount of antithrombin, and was designated as the antithrombin factor. The factor for a single comparison between tubes containing the same amount of thrombin determined at the same time, is known as a single series factor. At least three satisfactory series, not infrequently six, were run to obtain the antithrombin factor. An example of how these factors are obtained is given in Table 2.

To each specimen 1 drop of antithrombin was added to the varying drops of thrombin noted and allowed to remain in contact during the interval given and then 10 drops of fibrinogen were added.

If any one series gave a factor varying widely from the other series this was discarded, provided at least three other series remained which clotted in the suitable time, and the average of these was taken

for the antithrombin factor. This factor would, as a rule, fall close to the single series factor of the clots which clotted between ten and eighteen minutes.

For antithrombin determinations, specimens of blood must be diluted equally with oxalate solution, because the amount of the antithrombin will vary with dilution. A difference of from 5 to 4 c.c. of blood with 0.7 c.c. of oxalate will vary the factor from 1 to 0.87 +.

In the collection of specimens sometimes there may have been differences of 0.75 c.c. of blood.

TABLE 2.—Showing Method of Obtaining the Antithrombin Factor

Drops of Thrombin	Time Before Fibrinogen Added minutes	Clotting Time minutes	Clotting Time Control minutes	Single Series Factor
1	15	40 *	40 *	?
2	15	24	19	1.26 †
3	15	12 +	10	1.2 + †
4	15	9	7	1.28
5	15	6	5½	1.09
3	20	15	12	1.25 †
4	20	12	9½	1.26 †

* No clot in.

Second column shows interval thrombin and antithrombin remained in contact before fibrinogen was added.

Third column shows time clots formed in presence of antithrombin of case.

Fourth column shows time clots formed in presence of antithrombin of control.

The average of the series factors of those series that clotted in a desirable time (the marked † figures) is the antithrombin factor, which is 1.25.

(*F*). *Normal Antithrombin.*—The variation of antithrombin in normal human beings as determined by the method described above varies as is shown in Table 3. A study of from six to four normals on nine different occasions representing forty-eight observations on thirty-eight individuals was made. These normals were second year medical students, medical graduates, and laboratory attendants from 22 to 38 years of age, except that those tested on November 9 were four surgical patients recovering from hernia operations and fractures.

To obtain the degree of variation in the antithrombin factor the added time of a series of tests for the case with the highest antithrombin was divided by the lowest, and vice-versa. By excluding the case with the lowest antithrombin in each series the antithrombin factors will show less wide variations. In some series there was one case that had distinctly less antithrombin than the others. No one case had

distinctly more than the others. In using normals as controls the chances of variation in the antithrombin factor would tend to be plus rather than minus, provided the cases ranged in the vicinity of most of the normals.

If the cases of November 18 are excluded, because they were tested with an unsatisfactory fibrinogen solution, the greatest variation of the antithrombin factors in the other eight series is 1.34-0.73 +, and after excluding the case with the least antithrombin from each series the greatest variation is 1.21-0.82.

TABLE 3.—Normal Variations of Antithrombin

Date	No. of Cases	No. of Series of Determinations	Widest Variation in Single Series *	Variations Excluding Least Antithrombin †	Average Antithrombin Factor ‡	Factor Excluding Least Antitoxin §
July 22	5	5	1.30-0.77	1.15-0.86	1.15-0.86	1.15-0.86
Oct. 30	6	6	1.30-0.77	1.25-0.80	1.25-0.80	1.21-0.82
Nov. 7	6	5	1.35-0.73	1.11-0.89	1.25-0.80	1.11-0.89
Nov. 9	4	4	1.33-0.75	1.10-0.90	1.28-0.78	1.05-0.94
Nov. 11	6	7	1.38-0.72	1.26-0.78	1.3 -0.76	1.21-0.82
Nov. 18 ¶	6	7	1.6 -0.62	1.5 -0.66	1.46-0.68	1.3 -0.74
Dec. 9	4	4	1.4 -0.68	1.33-0.75	1.34-0.73	1.21-0.82
Jan. 6	6	5	1.25-0.80	1.25-0.80	1.20-0.82	1.16-0.85
Jan. 7	5	4	1.30-0.77	1.25-0.80	1.28-0.78	1.21-0.82
Average	5	5	1.35-0.73	1.24-0.81	1.28-0.77	1.17-0.84

* The widest variation in any single series of tests obtained by dividing the longest time of clotting of thrombin and fibrinogen in the presence of antithrombin by the shortest and the shortest by the longest. Figures in other columns obtained in similar way.

† Widest variation in any single series after excluding case with the least antithrombin.

‡ Average antithrombin factor of all series and cases

§ Average factor if case with least antithrombin is excluded.

¶ Tests of November 18 were run with an unsatisfactory fibrinogen solution, which probably explains why they show the widest variation.

It is felt that one can take for the widest extremes of factors from normals 1.34-0.73 + and for the usual variation 1.21-0.82.

In order to figure the antithrombin factor for a case, it is evident that it would vary considerably if we used a low or a high control. To be absolutely sure that we are dealing with pathological figures we must obtain an antithrombin factor below 0.55 or above 1.81. To be beyond the usual variation of normal, when we may be reasonably sure we are dealing with pathological conditions, we should obtain a factor below 0.68 and above 1.47.

The normals with low antithrombin should have been repeated to see if they were persistently low or fluctuated with diet, time of day, etc., but unfortunately this was not done. Some normals repeated on different days showed a rather constant relation to each other.

RELATION OF PROTHROMBIN TO ANTITHROMBIN

The prothrombin as well as the antithrombin was determined in this series of normals. One might expect that if the antithrombin was high, the prothrombin time would be relatively long, in that the greater amount of antithrombin present in the plasma would tend to delay the time of clotting on recalcifying the plasma, provided the other factors were equal. However, in comparing the prothrombin time of any given series with the antithrombin of the same series it was found that a short prothrombin time might go with the lowest or highest antithrombin. Among the diseased cases studied there are instances of even wider fluctuations than among the normals in the relation of prothrombin to antithrombin without occurrence of bleeding or thrombosis.

By Howell's theory one supposes that in normal blood the prothrombin and antithrombin are in balance which prevents intravascular clotting. It seems that there must be a relative excess of the antithrombin in the normal plasma, since considerable fluctuations may occur in the amounts of prothrombin and antithrombin without the occurrence of intravascular clotting. When blood is shed the balance is destroyed by the neutralizing effect of thromboplastic substance on the antithrombin.

By upsetting the balance of these factors, but to just what degree we cannot say, either spontaneous bleeding or thrombosis might occur. Decreases in prothrombin and increases in antithrombin are what might be expected with bleeding, with decreases of antithrombin and perhaps increase of prothrombin in thrombosis. Bleeding may of course be due to other factors of coagulation. Conditions not involving coagulation factors also cause bleeding and thrombosis.

In animals both the prothrombin and antithrombin content of the blood vary from that observed in the human being, so that their blood can not of course be used to control human, nor can serum be used as an antithrombin control to plasma since it usually contains less antithrombin than plasma.

In the normal dog numerous observations have shown that the prothrombin time varies from three to seven minutes while the antithrombin has been found to be about two and a half to three times the amount found in man. Though the antithrombin is greater[10] than in human blood, there is a decrease in prothrombin time which seems to indicate that the prothrombin is also increased. Here both factors are in balance but are in relatively greater amounts than in human

10. Though one speaks of antithrombin being greater in amount, we cannot actually determine the amount, but its power to inhibit the action of thrombin.

blood. Similarly in the cat, three observations showed the prothrombin time to be six to eight minutes and the antithrombin about half again as much as in man. In the rabbit the prothrombin time was from four to ten minutes and the antithrombin three times or more greater in amount than human. A single observation on hogs' plasma showed a relatively high antithrombin.

In considering prothrombin and antithrombin in cases one must not only consider the amounts but the relation of one to another, bearing in mind that the prothrombin test is relative. Are the two factors balanced; i. e., if increased are both increased, or is one increased and the other diminished?

ANTITHROMBIN AND PROTHROMBIN IN VARIOUS DISEASES

A study of antithrombin and prothrombin of ninety-three individuals with various diseases, making 121 observations, have been made and the results are given in the tables at the end of the paper (Tables 6 to 16).

The coagulation time of the whole blood was determined in many of the cases by a method described by Lee and White,[11] which is to allow 1 c.c. of the last blood drawn from a vein to clot in a tube 8 mm. in diameter. They found the normal coagulation time by this method was from five to eight minutes. Our tubes were slightly larger, 9 mm., and our normals ranged from six to about eleven minutes. Where figures for coagulation time are given in the tables they refer to this method. During this work, larger tubes and varying amounts of blood were used, but these gave less satisfactory results for ward work. Clotting took much longer owing to the larger surface area, and it was found that the tubes could not be moved at all without markedly altering the coagulation time. Temperature also had a more appreciable effect. Size of the needle, duration of the blood in the syringe, etc., are all factors that will vary the coagulation time. When technic other than Lee and White's was used, a control from a normal case was obtained at the same time, but the results were unsatisfactory. Where it was felt that there was a real decrease or increase in the coagulation time, the fact is indicated by a "+" or a "—", otherwise "N" for normal appears in the tables.

If the prothrombin time was above normal, the coagulation time of the whole blood was also increased. In some instances a delayed coagulation time occurred with a normal prothrombin time.

(*A*). *Cases with Abnormal Prothrombin.*—Table 4 shows the cases with delayed and accelerated prothrombin time.

11. Lee and White: Am. Jour. Med. Sc., 1913, cxlv, 495.

TABLE 4.—Cases with Delayed Prothrombin Time

Case No.	Observations	Diagnosis	Pro. T. minutes	Anti. T. minutes
92	2	Hemophilia	70-75	2.4 -2.3
83	2	Miliary tuberculosis, bleeding	39-44	1.4 -1.3
84	1	Miliary tuberculosis, bleeding	24	0.57
93	3	Benzol poisoning, bleeding	16-24	*
82	2	Amanita poisoning, bleeding	16-20	0.67-?
69	1	Pernicious anemia. No bleeding	15	0.73
22	1	Pernicious anemia. Thrombosis	19	0.56
88	1	Attacks of bleeding. Cause (?) During no bleeding	20	1.4
80	1	Rheumatic purpura	17	0.87
55	1	Chronic family jaundice	20	0.80
57	2	Jaundice cirrhosis	28-14	0.55-0.55
53	1	Jaundice, pneumonia. Uncinariasis	18	0.1
63	1	Jaundice, cancer pancreas	18	0.78
67	1	Jaundice 5 years. Cause? Bleeding	24	0.70
66	1	Congenital stenosis of bile ducts	40	.....

*Antithrombin determined but once when it was 1.1, at which time prothrombin was twenty-four minutes.

Cases with Upper Limits of Normal for Prothrombin

15	2	Typhoid	14	0.52-0.52
49, 50, 52	1 ea.	Pneumonia	14	?-1.1 -1.1
16 and 19a	1 ea.	Pernicious anemia	14	0.67-0.80

Cases with Accelerated Prothrombin Time. One Observation Each

Case No.	Diagnosis	Pro. T. minutes	Anti. T. minutes
37	Chronic myeloid leukemia, bleeding	2¾	0.75
36	Acute leukemia, bleeding	3	0.60
85	Acute leukemia (?) Pernicious anemia. Bleeding	5	0.45
40	Chronic splenomyelogenous leukemia	4	0.46
89	Myasthenia gravis; oozing blood from gums; bad pyorrhea	4	1.0
81	Purpura lesions of skin. Tuberculosis	4	0.66
75	Purpura lesions of skin. Question of aleukemic leukemia	3	2.2
21	Henoch's purpura	4	0.73
73	Pernicious anemia	4	1.1
74	Thrombosis. Syphilis	2	0.55

In some cases a prolonged prothrombin time may be explained by a corresponding increase in antithrombin, and, on the other hand, a shortened prothrombin time by a decrease in antithrombin, but as the tables show, there are cases in which a prolonged prothrombin time occurs, together with a diminished antithrombin and a shortened prothrombin time, with an increase in antithrombin. It is perhaps legitimate to conclude from this latter relation that the available supply of prothrombin in the blood, whether in solution, in the plasma, or stored in the platelets, may undergo variations in disease quite independently of the antithrombin content. The number of cases reported is too few to justify any positive deductions, but so far as they go they indicate that the supply of prothrombin was diminished in certain cases that were bleeding, as benzol poisoning, miliary tuberculosis, *Amanita* poisoning, and in certain cases of jaundice. The same is probably true in some cases of pernicious anemia and perhaps pneumonia, and in congenital hemophilia. In the latter condition, according to Howell, the prothrombin time is greatly delayed with increased or normal antithrombin content.

An actual increase in prothrombin is indicated clearly in the case of aleukemic leukemia (Case 81), but a relative if not actual increase (owing to diminished antithrombin) is shown in a number of cases, especially those with idiopathic thrombosis, some leukemias, and severe cases of typhoid fever.

Case 52 of poisoning due to fungus *Amanita phalloides* is reported in full by Clark, Marshall and Rowntree[12] and showed a slight delay in prothrombin time. A dog poisoned by them with this fungus showed a prothrombin time at the upper limits of normal.

(*B*). *Consideration of Other Factors in Relation to Prothrombin. 1. The Blood Platelets.*—Prothrombin is perhaps largely derived from these elements of blood as has been shown by Bayne-Jones,[13] among others, so that if they were diminished we might expect a diminished amount of prothrombin.

Varying the number of platelets in an oxalated plasma collected with certain precautions will vary the time of clotting on recalcification, being longer the fewer the platelets (Lee and Vincent[6]).

Thromboplastin is also derived from the platelets, so if they are lacking and the amount of prothrombin in solution is no greater than normal, one might expect a delayed prothrombin time.

That cases with very few plates have a prolonged bleeding time and spontaneous hemorrhages has been pointed out by Duke,[14] yet he

12. Clark, Marshall, and Rowntree: Jour. Am. Med. Assn., 1915, lxiv, 1230.
13. Bayne-Jones: Am. Jour. Physiol., 1912, xxx, 74.
14. Duke: The Archives Int. Med., 1912, x, 445

found by his method no striking changes in the coagulation of the whole blood.

The case (79) of benzol poisoning, belongs to this group. In this case the prothrombin time fluctuated with the number of plates. It suggested that if but few plates were present the prothrombin time would be lengthened. Similar results have been obtained by Hurwitz and Drinker[15] in experimental benzol poisoning.

In hemophilia the plates are normal or increased in numbers and yet the prothrombin time is delayed. That the plates are fixed and rendered unavailable is suggested by Fonio.[16]

Among the cases with diminished numbers of plates there are both abnormally high and low amounts of prothrombin.

It thus seems that the number of plates in the blood stream does not necessarily vary the prothrombin time and perhaps they must be very few to lengthen it. They do, however, seem to be an important element in connection with spontaneous bleeding in certain cases.

2. Calcium.—If it is necessary to add more calcium than usual to obtain the prothrombin time, one might suspect that there was something in the blood such as the bile pigments as suggested by Whipple and King[17] that bound some of the calcium and thus rendered it unavailable to transform prothrombin to thrombin, but we can see no reason why, if this took place, it should do so in delayed time. A case of this type is reported by Austin and Pepper and cases by Lee and Vincent.[18]

It is the available calcium that can act to transform prothrombin to thrombin that we are interested in from the point of view of coagulation and not the total amount in the blood.

The amount of calcium needed to obtain the prothrombin time of the normals and diseased cases was essentially the same, when the dilution of blood with the oxalate was the same, except in a very few instances which are cited below.

Of twenty observations on jaundiced cases, five cases showed a prothrombin time of over fourteen minutes and two of fourteen minutes.

Of these seven cases,[19] two (Cases 53 and 57) showed perhaps a tendency for, and one (Case 63) definitely, the need of an amount of

15. Hurwitz and Drinker: Jour. Exper. Med., 1915, xxi, 401
16. Fonio: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1914, xxviii, 313.
17. Whipple and King: Quoted by Whipple and Moss, see Reference 5.
18. Lee and Vincent: Personal communication; paper in print.
19. One of these seven, being Case 66, had a control with less oxalate solution, so whether more calcium was used to obtain the optimum time than would have been needed for a control, cannot be told.

calcium above that required for the controls to give the prothrombin time.

Case 63, a case of prolonged obstructive jaundice, required 5 drops of calcium to obtain the optimum time when the control took but 2 or 3 drops.

Of all the other cases studied no especially noteworthy changes in the optimum amount of calcium needed to clot the plasma were found except in Case 83, in which on the second observation the optimum amount of calcium was 4 drops while for the control it was 2 drops.

3. Fibrinogen.—Diminished amounts of fibrinogen can cause a loose clot and on this account perhaps favor bleeding. Whether such variations as can occur in the human body will cause an appreciable delay in the prothrombin time seems unlikely from the following facts:

Fibrinogen[20] was determined in Cases 82 and 54, and was above normal, yet the prothrombin time was slightly delayed in one of these. In one case (57) in which the prothrombin time was 14, and in Case 56 with a prothrombin time of 8, the fibrinogen was distinctly diminished.

A dog of Dr. Goodpasture's and two of Dr. Marshall's with phosphorus poisoning, a condition in which the fibrinogen is very low, showed on several observations a normal prothrombin time, though the antithrombin was low (0.60-0.14).

Another dog of Dr. Goodpasture's with experimental pancreatic disease showed, forty-eight hours before death, spontaneous bleeding from the rectum, low fibrinogen, and the antithrombin was 0.55. The prothrombin time was nine minutes, slightly above normal for a dog. The control dog gave five minutes.

In cases of cirrhosis of the liver Goodpasture[21] has shown that there exists a fibrinolytic ferment which may be a cause for bleeding. The two cases studied in which this substance was detected showed a normal prothrombin time in one, and an increased time in the other, so that it does not seem as if this ferment could be a cause for abnormal prothrombin time.

(C). Cases with Abnormal Antithrombin.—The determinations of prothrombin were followed in most instances by an antithrombin determination. If more than one control was used this is noted in the tables and the antithrombin factor is figured from their average. If the antithrombin factor of all the cases determined at the same time tended

20. Determinations of fibrinogen when given in the table of cases were made by the drying method described by Whipple (Am. Jour. Physiol., 1914, xxxiii, 50), normal being 350 to 600 mg. per 100 c.c. of blood. We are indebted to Drs. Marshall and Rowntree for the determinations in Cases 82, 57 and 54.

21. Goodpasture: Bull. Johns Hopkins Hosp., 1914, xxv, 330.

to be distinctly high or low, it suggested that an unusually low or high normal had been used. If this occurred it is noted.

Excluding the cases in which the prothrombin was above 14 and below 6, we notice that sixty-two had an antithrombin factor below 1; eight had 1 and thirty-one had above 1. Therefore, in the entire group of cases an antithrombin factor of less than 1 is commoner than above 1. Perhaps any person who is ill is more apt to have less antithrombin than when well. The chances of error from the variation of normals would tend to factors higher than 1 rather than lower.

Table 5 shows the cases with increased and diminished amounts of antithrombin.

A positive increase in antithrombin content of the blood is indicated in three cases only, all of which bled, namely, one of acute splenomyelogenous leukemia, aleukemic leukemia and congenital hemophilia while a relative excess is suggested in some of those cases in which the prothrombin is apparently diminished. The coagulation time in these cases when taken showed a delay except in the case of aleukemic leukemia in which there was obviously a compensatory increase of prothrombin. The reverse condition of a distinct diminution in antithrombin content was found, especially in cases of severe typhoid fever, certain leukemias, anemias and thrombosis. In such conditions, if prothrombin and other factors are normal or perhaps increased, there should be a diminished clotting time and a tendency to the formation of thromboses. A distinct diminution of antithrombin in some cases that bleed may be a compensatory effect due to the bleeding from causes other than antithrombin or prothrombin.

Fifteen cases of typhoid fever, on which twenty-four observations were made, were studied especially with the thought that some of them would develop a thrombosis, and that one might be able to predict such an occurrence by a decrease in the amount of antithrombin. Fortunately for the patients' sake none of the cases developed a definite thrombosis.

Low factors frequently occurred, the lowest in the two sickest cases. The two highest occurred in mild cases in which the temperature was normal or nearly so.

All the antithrombin factors of the nineteen cases grouped in the tables under secondary and pernicious anemia are below 1, except in one case of pernicious anemia which had 1.2 and a prothrombin that was abnormal (four minutes) and Case 34 of secondary anemia with frequent hemorrhages. There are ten cases with factors below 0.75, six of which are from the eight cases of pernicious anemia. Nearly all the cases that had a distinct anemia and a normal prothrombin, tend to have a low antithrombin. There are, however, exceptions.

TABLE 5.—Cases Having Antithrombin Beyond the Conceivable Limits of Normal

Case No.	Diagnosis	Pro. T. minutes	Anti T. minutes
Cases Having Antithrombin Below 0.55			
73	Thrombosis, idiopathic (?)	2	0.55
67a	Prolonged jaundice; recently bleeding	10	0.54
57	Jaundice, cirrhosis; two observations	28-14	0.55-0.55
15	Typhoid; very sick; purpura; three observations	14, 14, 9	0.52-52-53
40	Splenomyelogenous leukemia, chronic	4	0.46
8	Typhoid; purpura; 48 hrs. before death.	12	0.46
85	Pernicious anemia (?), acute leukemia, bleeding	5	0.45
Cases Having Antithrombin Above 1.81			
41	Acute splenomyelogenous leukemia; very slight bleeding; two observations	10-10	2.4 -1.9
81	Aleukemic leukemia (?); purpura	3	2.2
92	Hemophilia	75 70	2.4 -2.3
Cases with Antithrombin 0.68 or Below			
1, 2, 5b, 13 15b and 15e	Typhoid; five cases	6-11	0.57-0.67
17, 18, 19a	Pernicious anemia; one with thrombosis; five cases	8-19	0.56-0.67
74, 75b and c	Purpura; anemia; two cases	8-14	0.60-0.66
29, 30, 32	Secondary anemia; three cases	6-12	0.57-0.65
58	Jaundice; endocarditis; anemia; infarcts	10	0.61
68	Thrombosis, traumatic after leg amputation	10	0.67
36	Acute leukemia	3	0.60
82	Amanita poisoning; bleeding	20	0.67
84	Miliary tuberculosis; bleeding	24	0.57
Cases with Antithrombin 1.47 or Above			
12	Mild typhoid	9	1.8
61a, 61b, 65	Jaundice; two cases; long duration in one; the other catarrhal	6- 8	1.7 -1.8
47, 44	Positive Wassermann, two cases; one with large liver and nephritis; the other showed only fever	12- 6	1.64-1.73
78	Purpura; dyspituitarism	8	1.78

Drinker[22] has shown that with rapid progressive hemorrhage in animals the antithrombin falls and two observations on animals made by us have shown the same. In Case 10, whose hemoglobin was 80 per cent. and fell in four days to 30 per cent. from hemorrhage, the antithrombin at this latter time was 0.96; but what it was previously we do not know. We might have expected it to be low from the anemia as well as from the sudden loss of blood.

Among the miscellaneous cases the average antithrombin is over 1, as a contrast to the anemias. Some of these cases were studied because of enlarged livers, in view of the fact that the liver is important in the formation of antithrombin.[23] Among the clinical cases, however, we have many types of liver disease with antithrombin varying from 0.55 to 1.7, and no definite relationship can be seen between the different liver conditions and the amount of antithrombin.

Does antithrombin vary with the amount of fibrinogen? In anemia the fibrinogen is often low (Whipple[20]) also in typhoid (D'Oelsnitz et al.[24]) as is the antithrombin. In the dogs with phosphorus poisoning and in Dr. Goodpasture's dog with pancreatic disease, both the fibrinogen and antithrombin were low. Case 56, with a low fibrinogen, had antithrombin 1.1. In Case 54 of pneumonia with increased fibrinogen, antithrombin was normal. Whether antithrombin usually falls with diminution in the amount of fibrinogen, we have not enough data at present to say.

Syphilitic serum has been shown by Hirschfeld and Klinger,[25] also Frankel and Thiele[26] to have the power when mixed with proper amounts of coagulation materials to inhibit coagulation. This, however, is probably not due to antithrombin, as none of the five cases in our series with a positive Wassermann showed any special variation from normal.

Dochez[27] has made a careful study of the coagulation time in pneumonia and found it increased at the height of the disease and suggested that it was due to an antithrombin increase. Actual antithrombin increase did not exist in the two cases of pneumonia studied; the factors in both were 1, while the prothrombin was well at the upper limits of normal; so there may have been a slight relative increase.

(Studies at the Massachusetts General Hospital are now being made on the factors of coagulation in pneumonia and will be reported at a later date).

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22. Drinker, K. R. and C. K.: Am. Jour. Physiol., 1915, xxxvi, 305.
23. Denny and Minot: Am. Jour. Physiol., 1915, xxxviii, 233.
24. D'Oelsnitz, et al.: Bull de l'Acad. de méd., Paris, lxxiii, 282.
27. Dochez: Jour. Exper. Med., 1912, xvi, 693.
25. Hirschfeld and Klinger: Deutsch. med. Wchnschr., 1914, xl, abstr. of Am. Med. Assn., 1914, lxiii, 1241.
26. Frankel and Thiele: München. med. Wchnschr., 1914, lxi.

CONSIDERATION OF THE FINDINGS IN CERTAIN GROUPS OF CASES

Kocher,[28] Kollman and Godsky[29] and others have reported changes in the coagulation time of the blood in thyroid disease. Two cases of Graves disease studied, not included in this series, showed no very striking changes in their prothrombin and antithrombin content.

Howell[1] found no abnormality in the prothrombin or antithrombin content of the blood in the cases of purpura which he studied, and we found no significant changes in our cases, except in two (Cases 78 and 81) the antithrombin was distinctly high, in one the prothrombin time was normal, and in the other decreased. Whether the increased antithrombin could have been the cause for the purpura in these two cases can only be told after further research on the amount of antithrombin in relation to prothrombin that may cause bleeding.

Among the leukemia cases high prothrombin (decreased prothrombin time) frequently occurred. In some of the leukemias this might be due to the increased number of white cells in the circulation which yield thromboplastic material, but some of the cases with an equal or greater number of cells had a normal prothrombin time.

The white cells from Case 41, with antithrombin 2.2, were isolated and tested to see if they showed any antithrombic activity, but none was found. These cells, like any white cells, exhibited thromboplastic activity.

In three cases of spontaneous thrombosis Howell found that there was a low antithrombin with a normal prothrombin. The antithrombin in his cases expressed as antithrombin factors vary from 0.3— to 0.4+.

One case (73) of idiopathic thrombosis gave a low antithrombin factor (0.55) but also the highest prothrombin of any case, two minutes. A case of pernicious anemia without fever, developing thrombosis after splenectomy, gave a low antithrombin, 0.56, slightly lower than the other cases of pernicious anemia, with a low prothrombin (19 minutes). The serum of this case at necropsy was tested for antithrombin and found to be 0.4 (normal oxalated plasma as control). We do not know how serum obtained at necropsy may vary from normal blood in its antithrombin content. Serum as a rule has slightly less antithrombin than oxalated plasma. One case of cardiac disease whose serum was tested about the same time after death as that of the pernicious anemia case, gave a factor of 0.9. It thus seems that the serum from this pernicious anemia case after death contained certainly less antithrombin than serum of a patient whose antithrombin was presumably normal before death.

28. Kocher: Arch. f. klin. Chirurg., 1912, xcix, 280.
29. Kollman and Godsky: Ztschr. f. klin. Med., 1914, lxxix, 362.

The other cases of thrombosis studied were probably not of the idiopathic type. The antithrombin in these varied between 1.46 and 0.67.

It is quite possible that none of the cases we have studied is of the same type as those studied by Howell, and until we know more about such cases we cannot tell what type it is that has a strikingly low antithrombin content.

Cases with quite wide changes in the prothrombin and antithrombin content from normal and in the relation of these two substances to each other, may or may not bleed. All cases with spontaneous bleeding are not due to these factors.

Of the cases studied with spontaneous bleeding and hemorrhagic tendency, if the factors were abnormal at all, there was usually a decrease of prothrombin, with more usually the antithrombin factor above than below 1. The few cases with strikingly high antithrombin content all had some signs of spontaneous hemorrhage.

Cases of bleeding occurred with increased prothrombin and with antithrombin above or below 1. In such instances perhaps there were other factors at work to cause the bleeding and the increased prothrombin was a compensatory process to shorten the coagulation time and stop the hemorrhage.

SUMMARY AND CONCLUSIONS

1. Prothrombin time, tested by the method used, varies normally from six to fourteen minutes.

2. Technic and difficulties of the antithrombin test have been described.

3. The antithrombin factor is the most satisfactory method for the comparison of amounts of antithrombin.

4. Antithrombin varies normally. The antithrombin factor must be below 0.55 and above 1.81 before one can be absolutely sure that the amounts are abnormal; one may be reasonably sure that the amounts are abnormal if the factors are below 0.68 or above 1.47.

5. In some cases a prolonged prothrombin time may be explained by a corresponding increase of antithrombin and a shortened prothrombin time by a decrease. There are cases which suggest that the available supply of prothrombin in the blood may undergo wide variations in disease independent of the antithrombin content. Certain cases of bleeding and of jaundice, also hemophilia, as well as others, seem to have a diminished supply of prothrombin. Actual increase of prothrombin does occur, as is indicated in a case of aleukemic leukemia, and in some animals as compared to the human being. Relative increase is shown in a number of cases, especially thrombosis and some leukemias.

6. Prothrombin time does not always vary with the platelet count.

7. Cases exist in which more calcium than usual is needed to obtain the prothrombin time.

8. The amount of fibrinogen in human blood probably does not vary sufficiently to alter appreciably the prothrombin time.

9. A positive increase of antithrombin is indicated in three cases. A relative excess is suggested in some cases in which the prothrombin is apparently diminished. Diminution in antithrombin was especially found in cases of severe typhoid fever, certain leukemias and anemias and thrombosis, and in some cases associated with a low fibrinogen content.

10. Cases of spontaneous bleeding occurred with normal coagulation factors. Others showed a low prothrombin, usually but not always associated with a relatively high antithrombin. The three patients with a very high antithrombin, all bled.

Since this article was written Hurwitz and Drinker have published (THE ARCHIVES INT. MED., 1915, xv, 733), a paper entitled "Factors of Coagulation in Primary Pernicious Anemia." While we found an abnormal antithrombin content in our cases of pernicious anemia, they did not. This may be due to differences of technic. They state, "Prothrombin is diminished slightly in all cases of pernicious anemia." Our findings agree, with the exception of two cases, in which there was an increase.

It is a pleasure to thank Dr. Howell for his supervision of this work and to thank the members of the staff of the Johns Hopkins Hospital for allowing us to study their cases.

188 Marlboro Street—285 Marlboro Street.

TABLE OF CLINICAL MATERIAL

Cases from the wards of the Johns Hopkins Hospital, except the following: No. 83 was at Bay View Hospital and Case 30, one of Dr. Boggs', to whom we are indebted for the opportunity to study these two cases.

Cases 27, 85 and 86 were private patients of Dr. Thayer.

Cases 67, 88 and 91 were seen by Dr. Howell in consultation.

Case 37 was one of Dr. Judd's, reported in Jour. Am. Med. Assn., 1915, lxiv, 1630.

We are much indebted to Drs. Thayer, Howell and Judd for being able to study the above cases.

The blood from the patients was obtained by one of us in all instances except Case 37, which was obtained for us with our materials by Dr. Judd.

The date refers to the year March 30, 1914 to March 29, 1915, unless 1915 is stated.

The clots of the whole blood retracted unless stated.

Platelet counts were done by Wright and Kinnicutt's method.

TABLE 6.—Typhoid Fever

Proved by positive Widals or blood cultures. All these cases had a hemoglobin of over 80 per cent., unless stated.

No.	Date	Week of Disease		Pro-thrombin	Anti thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
1	June 10	3	Fever began to break June 13. Perforation of bowel occurred June 20. Fever up to 101 F., until death, July 20	8	1.0	.....	6
1a	June 27	5	.....	8	0.67	.....	8
2	July 13	3	Mild case. Fever began to break July 16. Uneventful convalescence except for slightly tender toes	6	0.63	N	6
2a	July 20	4	.....	8	0.70	Sl. +	6
3	July 22	3	Fever began to break July 30; July 25-30, hemorrhages, small, from bowel	6	0.81	N	6
4	Oct. 16	9	Normal temperature after October 16. Discharged November 13, after uneventful convalescence	8	1.15	.....	10
5	Oct. 21	3	Fever begins to break October 24, but reaches to 105 F., not being normal till November 22. No complications	8	1.15	.....	10
5a	Oct. 23	4	.....	6	0.75	5½	8
5b	Nov. 11	7	.....	8	0.65	.....	12 *
6	Oct. 28	3	Hemoglobin, 63 per cent.; R. C., 3,712,000. Fever began to break November 3. Temperature close to normal, Nov. 20-30, then a relapse until December 20. No clot retraction	10	0.57	10	9-12 †
7	Oct. 28	3	Fever begins to break November 2-7, running up to 100.5 F. until Dec. 22	10	0.74	8	9-12 ‡
8	Oct. 29	3 +	Severe toxic case; October 24 urticaria and purpura appeared, growing worse until death, October 30. No necropsy; *plates plentiful in smears*	12	0.46	6 +	8
9	Nov. 23	4	Perforated November 20; died November 24. Fever 101-103 while in hospital	8	0.85	5	14

10	Oct. 14	2+	October 10, 1,000 c.c. rectal hemorrhage; several smaller hemorrhages until October 14; hemoglobin in five days reduced from 80 to 30 per cent. Mild relapse October 27-November 4, without further complications	8	1.1	6½	12‡
11	Oct. 16	5	Mild case. Temperature 100 F. after October 18, and normal after October 27	6	1.0	.....	10
12	Dec. 17	3	Uneventful case. Temperature normal January 8 and low after December 17	9	1.80	7	14§
13	Nov. 9	3	Fever high until November 19. Relapse December 1, at which time a question of peritonitis was raised; discharged well January 1	10	0.57	.....	8
14	Dec. 9	3	Mild case. R. C., 6,664,000. No fever after December 16	8	0.92	8	8¶
15	Oct. 14	3	Husband of No. 6. Rectal hemorrhage, October 15 and 18, reducing hemoglobin 10 per cent.	14	0.52	11½	12‖
15a	Oct 21	4	October 22, sloughing decubitus developed; others occurred later	14	0.52	10	10**
15b	Nov. 6	6	November 4. Arms became swollen and urticaria developed	10	0.64	8	10
15c	Nov. 11	7	Question of axillary thrombosis was raised, left arm worse than right	9	0.53	.....	6-11††
15d	Nov. 18	8	Purpura of arms and face developed, November 6, increased by tourniquet	11	1.00	.....	8-12‡‡
15e	Dec. 9	11	Urticaria and slight purpura persisted with fluctuations until November 15, accompanied with and followed by scaling of skin all over body. Fever reached normal, November 6; gradually rose again until November 14, then slowly fell to 100 by December 9, and fluctuated near normal until discharge. Acute nephritis developed in December	11	0.65	.....	13 9¶

* Six controls. † Two controls. ‡ Two controls. § Other cases run with this had antithrombin 1.3 and 1.15. ¶ Four controls.
‖ Two controls that were equal in antithrombin content. ** One of controls of October 14. Other cases had high antithrombin
†† Six controls. ‡‡ Six controls.

TABLE 7.—Pernicious Anemia

All have typical blood smears.

No.	Date	Red Count	Hgb. (Sahli) Per Cent		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
16	May 13	4,640,000	75	Bad pyorrhea. No fever. Spleen not felt	14	0.80	N	12
17	July 6	1,900,000	42	Bad pyorrhea. Slight fever. Spleen easily felt	10	0.60	N	10*
18	July 13	626,000	25	Continued fever often 103 F. Died Sept. 2	8	0.62	N	6
19	July 20	1,000,000 (Decreased fragility of red cells)	25	Continued low fever. Combined sclerosis of cord. Nov. 14, transfused 500 c.c.	8	0.72	8	6
19a	Nov. 18	1,608,000	33	Highest red count Nov. 19, 1,608,000, with blast crisis	14	0.67	17	9-12†
20	Oct. 17	1,872,000	35	Large spleen. No fever	10	0.65	.....	8
21	Dec. 2	2,080,000	55	Numbness hands and feet. Large spleen. Slight fever	4	1.2	5	11-14‡
21a	Dec. 2	.....	.....	.....	4	.....	.....	.....
22	Dec. 12	1,584,000	37	Very slight fever. Spleen felt (poor clot retraction)	15+	0.73	10+	7§
23	Oct. 21	1,312,000 (Slightly increased fragility of reds)	33	Liver and spleen easily felt. Question of myxedema. Question of family jaundice. (Labor, Oct. 4) Note also Cases 69 and 85	10	0.73	9	10

*Three other cases had antithrombin over 1. †Six controls. ‡Two controls. §Two other cases had prothrombin of twelve and eight minutes.

TABLE 8.—Secondary Anemia

No.	Date	Red Count	Hgb. (Sahli) Per Cent.		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
24	May 11	2,438,000	25	Cancer of stomach. Advanced case. White count 8,000	8	0.84	Sl. +	8
25	June 8	4,112,000	40	Positive Wassermann. Osteomyelitis of rib; culture showed paratyphoid organism. Very large spleen. White count 4,000	6	0.95	8	6
26	July 22	"	65	Congenital cystic kidneys. Chronic nephritis. Nosebleed frequent for eight years. Fever 99-101 F.	8	0.90	N	6
27	July 21	1,700,000	25	High fever; very large spleen; liver palpable. Diagnosis (?)	10	0.85	Sl. +	6
28	Dec. 2	4,184,000	80	Banti's disease with ascites	11	0.80	11	11 *
29	Oct. 19	1,812,000	36	Long standing anemia due to possible anaplasma in blood. White count 19,450	10	0.65	7	10 †
30	Oct. 23	2,824,000	40	Severe chronic nephritis. Albuminuric retinitis. Uremia. Myocardial insufficiency. Discharged improved January 13	12	0.57	11	8
31	May 22	4,000,000	65	Hodgkins' disease with marked enlargement of mediastinal nodes	10	0.90	. . . .	6 ‡
32	July 9	4,100,000	72	Aneurysm, thoracic aorta, positive Wassermann. Myocardial insufficiency; ascites. Systolic blood pressure, 0,90	6	0.65	. . .	8
33	Oct. 9	"	70	Syphilis of central nervous system	10	0.75	9	6
34	Feb. 22	2,500,000	40	Frequent small hemorrhages from nose. Diagnosis. Note other cases of secondary anemia under purpura, leukemia, etc.	12	1.31	"	6

* Two controls. † Three other antithrombin were 1.1, 1.8 and 1.3. ‡ Two other cases of prothrombin were (1) eight and (2) ten minutes.

TABLE 9.—Leukemia

No	Date	Red Count	Hgb. (Sahli) Per Cent	White Count		Prothrombin	Antithrombin	Coagulation Time minutes	Prothrombin Control minutes
35	Dec. 17	2,856,000	50	930,000	Fairly acute splenomyelogenous with fever	9	1.2	Sl. +	14
36	Nov. 17	?	80	7,000	Ninety per cent. small lymphocytes acute type	3	0.60	—	8-12*
37	Dec. 12	1,000,000	30	300,000	Acute myelogenous. died of hemorrhage, Dec. 14. See under "Bleeding Cases"	2¾	0.75	.....	7
38	May 22	2,792,000	54	352,000	Chronic splenomyelogenous	8	1.0	N	6
39	July 6	4,430,000	68	368,000	Chronic splenomyelogenous. Developed hemorrhagic purpura in September and died	10	1.0	N	10
40	July 20	2,320,000	47	187,200	Chronic splenomyelogenous with arteriosclerosis	4	0.46	.	6 +
41	April 29	2,880,000	50	362,000	Acute splenomyelogenous. High fever. Slight bleeding from nose. Question of bleeding to internal ear. No further bleeding before patient left hospital	10	2 4	?	6†
41a	April 30	2,880,000	50	362,000	..... Note also Cases 81 and 85	10	1.9‡	.....	6

* Six controls. † One other case antithrombin = 1.3. ‡ One other case antithrombin = 1.2.

TABLE 10.—Miscellaneous

Hgb. over 80 per cent. unless stated

No.	Date		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
42	June 4	Chronic nephritis; chronic alcoholism. Large liver	6 +	1.1	N	8
43	July 9	Myocardial insufficiency; arteriosclerosis; ascites; liver with slight passive congestion at autopsy. Hgb. 73 pct	8	0.71	N	8 *
44	Oct. 19	Positive Wassermann. Chronic nephritis; arteriosclerosis. Myocardial insufficiency, with large liver. Red count 6,600,000. Hemoglobin 95 per cent.	12	1.64	8	10 †
45	Oct. 21	Myocardial insufficiency with liver to umbilicus. Dilated aortic arch. Aortic and mitral disease.	10	1.30	9	10
46	May 1	Typical angioneurotic edema with urticaria	8	1.0	N	14
47	July 6	Positive Wassermann. Fever to 102 F. for two weeks, gradually reaching normal July 10. White count 4,300	12	1.7	Sl. +	10 ‡
47a	July 7	.....	10	1.2	N	10
48	Dec. 9	Arteriosclerosis. Sinusitis. Chronic nephritis (?)	10	0.85	N	9 13 §
49	Oct. 19	Positive Wassermann. Consolidation of lower right lobe of lung, perhaps pneumonia; thought to be tuberculosis. No crisis. Discharged against advice when temperature was still 99-102 F.	14	1.1	10	10 ¶
50	Oct. 13	Lobar pneumonia; typical crisis October 16.	14 +	1.1	14	10
51	Jan. 13	Preeclamptic. Delivered of premature baby this morning. In past four days has had 2 3 convulsions. Bled 500 c.c. this morning.	6	1.0	5	6

* Three other cases have low antithrombin. † Case 29 had antithrombin 0.65. ‡ Case 17 had antithrombin 0.60 and Case 59, 1.7
§ Four controls. ¶ Other prothrombin times, 8 12.

TABLE 11.—JAUNDICE.

Hemoglobin over 80 per cent unless stated. (A) SLIGHT

No.	Date	Remarks on Blood		Prothrombin	Antithrombin	Coagulation Time minutes	Prothrombin Control minutes
52	April 22	W. C., 23,160	Lobar pneumonia. Positive Wassermann. Crisis, April 23	14	?	+	6*
53	May 12	R. C., 4,000,000; hgb., 40 per cent.; W. C., 4,200. Plates normal in smears	Positive Wassermann. Uncinariasis. Bronchopneumonia. Large spleen. Bradycardia. Fever to 105 F. on the 12th and 13th. Crisis, 13th. Jaundice gone May 23	18	1.0	15	12
53a	June 1			8	0.9	N	6
54	Oct. 28	W. C., 15,680; hgb., 65 per cent. Fibrinogen, 700 mg. per 100 c.c. blood	Lobar pneumonia. Lysis, October 27-30. Liver large	12	0.90	13 +	9-12 † 8
55	March 30	R. C., 2,820,000; hgb., 55 per cent. Plates in smears appear normal	Congenital family jaundice. Ulcers on legs. Slight jaundice	20	0.80	+	
55a	May 29	Hgb., 80 per cent.	Almost no jaundice present	10	1.1	?	8
56	Oct. 9	W. C., 11,700. Fibrinolytic ferment present. Fibrinogen diminished 280 mg. per 100 c.c.	Gout. Atrophic cirrhosis of liver. Arteriosclerosis. Died, "hepatic insufficiency," October 28	8	1.1	7	6
57	Nov. 23	Fibrinolytic ferment present	Cirrhosis of liver. Plates appear in normal numbers in smears.	28	0.55	15 +	14
57a	Dec. 2	Fibrinogen, 211 mg. per 100 c.c.	Very little jaundice now	14	0.55	12 +	11-12 †
58	Oct. 14	R. C., 3,100,000; hgb., 64 per cent.; W. C., 21,000	Acute and chronic endocarditis. Broken compensation with ascites. Pulmonary infarcts. Fever 100-101 F. till October 20	10	0.61	9	12 †

(B) MODERATE JAUNDICE

59	May 25	.....	Catarrhal jaundice, age 10	6	0.75	N	8
60	Oct. 23		Catarrhal jaundice, age 17	6	0.74	7	10
61	July 6	W. C., 17,000	Catarrhal jaundice, age 21	6	1.7	N	10‡
61a	July 7	.....	Jaundice gone by July 22	8	1.8	N	8
62	July 9	.....	Myocardial insufficiency. Chronic nephritis. Liver large	8	0.70	N	8

(C) DEEP JAUNDICE

63	May 29	.....	Cancer of head of pancreas. Metastasis to liver (?) Duration weeks	18	0.78	Sl. +	6
64	June 10	R. C., 4,100,000; hgb., 42 per cent.	Cancer of stomach with liver metastasis. Fever up to 100 F.	6	0.93	—	6
65	March 18	R. C., 3,400,000; hgb., 72 per cent.; W. C., 7,500	Stenosis common bile duct due to stone proved at operation, March 20. Jaundice for five years with short periods of relief. Began to bleed from gums three days after operation; developed peritonitis from which he died, March 27; bleeding from nowhere else and was not severe	6	1.73	19	6
65a	March 24	.....	.....	12	1.0 +	21	9
66	March 11	.....	Congenital stenosis bile ducts. Baby	40	.....	.....	8
67	Feb. 25	?	Woman, aged 29. Jaundiced for seven years; has been operated on for gallstones; none found; one year ago bled badly when tooth pulled; two months ago bled from gums for about two weeks; bleeding has now been going on one week and bleeds when she scratches herself	24	0.70	28	8
67a	March 15	?	Given kephalin for the past two and one half weeks, no bleeding for ten days	10	0.54	14	6
67b	April 1	?	No kephalin for past two weeks and now bleeding a little from gums	12	1.0	18	6
	May 18		Less jaundice. No kephalin since last note. No bleeding	15	0.8	23	8

* No other cases. † Two controls ‡ 67b antithrombin, 0.60.

TABLE 12.—Thrombosis

Hemoglobin over 80 per cent. unless stated.

No.	Date		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
	1914					
68	Oct. 9	Of femoral artery and vein; traumatic etiology.....	8	1.46	6	6
68a	Oct. 16	After amputation of leg patient died three days later.....	10	0.67	5	10
69	Nov. 24	Pernicious anemia; splenectomy Nov. 11. Thrombosis of femoral vein recognized for eighteen hours. Nov. 17, red blood cells, 3,465,000; hemoglobin, 75 per cent.; plates very plentiful in smears after splenectomy.	19	0.56	.....	14
69a	Nov. 30	Patient died from pulmonary embolus Nov. 30. Confirmed at necropsy, which showed thrombosis, also thrombosis of femoral, splenic, portal veins and inferior vena cava. Combined sclerosis of cord. Pernicious anemia. There was no fever from November 11 to November 29. "Blood" five hours after death fluid due to autodigestion, as it would clot only on addition of solution of fibrinogen. This "blood" diluted with oxalate is what was tested, the control being normal blood diluted with oxalate as usual.	.....	0.40	.....	.....
	1915					
70	Jan. 15	Private case, Dr. Boggs. Frequent attacks of idiopathic thrombosis. No attack for over six months. 0.0001 gm. of hirudin given intravenously after blood drawn.	7	1.30	8	8
70a	Jan. 16	Temperature 105 F.; severe reaction; well in forty-eight hours.	9	1.25	.....	9
71	Jan. 16	General paresis. Salvarsan intravenously five days ago. Intraspinal mercury albuminate yesterday; today evidence of venous thrombosis of femoral vein.	11	1.0	8	9
72	Jan. 13	Operated for inguinal hernia three weeks ago; about ten days ago developed cough with bloody sputum; pain in chest; bronchopneumonia infarct (?)	8	1.30	6	6
73	April 17	Idiopathic thrombosis; began with a femoral thrombosis two weeks ago, then cerebral. Comatose.	2	0.55	?	8

TABLE 13.—Purpura with Skin Lesions

No.	Date	Blood	Plates		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
	1914							
74	May 8	Hgb., 50 per cent. W. C., 10 15,000. R. C., (?)	Normal in smears	Generalized tuberculosis of sixteen months duration. Fading purpuric spots on legs	4	0.66	.....	8
75	June 1	.. ..	June 3 180,000	Henoch's purpura with recurring abdominal attacks and lesions on skin	4	0.73	.....	6
75a	June 4	.. .	..	Many spots gone. Angioneurotic edema at times	6	0.72	N	8
75b	July 6	Hgb., 70 per cent.; R. C., 4,300,000	150,000	Fresh crops of spots fourteen hours ago	8	0.60	N	10
75c	Oct. 13	.. . .	60,000	Abdominal attack and many fresh minute spots all over body (Poor clot retraction)	8	0.63	8	10
76	Oct. 2	Red cells, 4,080,000. Hgb., 55 per cent.	240,000	Male, 62 years of age. Lymph glands and spleen enlarged. Chronic diarrhea, achylia gastrica; continued low fever for two years. Very frequent outbreaks on his legs of purpuric spots; spots, present October 2; fresh crop, Oct. 29	10	0.71	8	10

TABLE 13. PURPURA WITH SKIN LESIONS *(Continued)*

Hemoglobin over 80 per cent. unless stated. All clots retract well.

No.	Date	Blood	Plates		Prothrombin	Antithrombin	Coagulation Time minutes	Prothrombin Control minutes
77	Dec. 12	.....	Plentiful in smear	Chronic nephritis with albuminuric retinitis; mild uremia. Purpuric spots on legs developed, December 11	12	0.70	9	7
78	July 7	.....	Appear normal in smears	Female with male characteristics. Dyspituitarism. Cyst of thyroid. Blood pressure, systolic 180. Frequent attacks of epistaxis and small purpuric spots on arms, present July 7	8	1.78	.....	8†
79	June 8	.....	.....	Female giving history of repeated attacks of purpuric spots on skin. None present June 8	6	1.2	N	6
80	March 11	?	?	Rheumatic purpura; child; spots nearly gone	17	0.87	.....	?
81	1915 April 21	A high per cent. of large lymphocytes. W. C., normal	?	Big spleen. Question of aleukemic leukemia. Has had several attacks of purpura and has one at present Note also Cases 8 and 15	3	2.2	9	6

* Case 59, antithrombin, 1.7. Case 46, 1.7. † Other cases antithrombin 1.1 and 1.80.

TABLE 14.—Hemorrhagic Cases without Purpuric Spots on Skin

No.	Date	Blood	Plates		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
82*	Oct. 2	R. C., 6,456,000. Hgb., 90 per cent. W. C. 16,720. Fibrinogen, 600 mg. per 100 c.c.	388,000	Poisoning from the fungus *Amanita phalloides*, eaten about September 14. September 28 bleeding from gums began, continued intermittently until death. Bleeding from rectum began October 7, continued intermittently till death, October 11. Functional kidney tests showed diminished function of kidney. Autopsy showed central necrosis of liver; epithelial necrosis of kidney, acute enteritis and colitis hemorrhagic bronchopneumonia	20	0.67	12	10
82a	Oct. 3				16		11	8-10†
83	Dec. 2	Hgb., 30 per cent. R. C., 1,500,000	60,000 Plates appear diminished in smears but not absent.	Bleeding from nose, rectum and genito urinary tract, which began about November 25 and persisted until death about December 12. Autopsy showed miliary tuberculosis with enlarged liver. After the blood clotted it would reclot on breaking up several times	44	1.3	35	11-12‡

* Case reported by Clark, Marshall and Rowntree.

TABLE 14.--Hemorrhagic Cases without Purpuric Spots on Skin *(Continued)*

No.	Date	Blood	Plates		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
83a	Dec. 9	.....	112,000	.....	39	1.4	30	9-13 †
84	Feb. 22	R. C., 3,200,000. Hgb., 60 per cent.	? W. C. 6,600	At necropsy, miliary tuberculosis. Duration 2+ months. At onset, severe nosebleeds; persisting off and on until death about February 28	24	0.57	.....	6
	1915							
85	April 21	R. C., 1,500,000. Hgb., 30± per cent. W. C., (?)	?	Splenectomy one month ago for aplastic anemia with marked improvement until severe bleeding of nose began a few days ago; now thought to be acute leukemia. No record if clot retracted or not	5	0.45	6	6
37	Dec. 12	See under leukemia	Plates absent in smears	Acute lymphatic leukemia of six weeks' duration. December 6 began to have oozing nosebleed which persisted. December 10, hemorrhage from stomach and rectum. Direct transfusion from donor of same isoaglutinin group after specimen oftained for testing coagulation, but hemorrhages persisted and patient died December 13	2¾	0.75	?	7 §

41	April 29	See leukemia	.....	Acute leukemia; slight nosebleed and question of bleeding to internal ear	10	2.4	?	6
41a	April 30	.....	.....	.....	10	1.9	.....	8
86	July 15	Hgb., 70 per cent.	Normal in smears	Prolonged oozing of blood from nasopharynx after operation	6	0.78	N	6+
87	March 5	"Normal"	?	Trauma right hand two years ago; since then intermittent hemorrhagic swelling of area every two to three weeks. No other hemorrhage. No hemorrhage for two months; during this time has had kephalin, but also a splint	11	1.23	14	7
88	April 6	.....	Plates (?)	No hemophilic history; age 24 (?) Was well until after operation on tonsils one year ago, when he nearly bled to death. Has bled very severely several times since. Last, two months ago. No anemia now or bleeding. No record if clot retracted or not	19	1.4	20	6
89	July 13	Hgb, 100 per cent.	Plentiful in smears	Myasthenia gravis; mild oozing from gums, with bad pyorrhea	4	1.0	6	6¶
90	June 8	Normal	?	Large hematoma on leg. Traumatic	8	0.90	N	6
91	Oct. 28	.....	.....	Gives a history of bleeding easily and for rather long time if cut. Not evident October 28	12	1.0	9	12

† Four controls. ‡ Two controls. § Case 69, prothrombin, twelve minutes. Case 22, fifteen minutes. ¶ Three other cases had prothrombin time six to eight minutes.

TABLE 15.—Hereditary Hemophilia

No.	Date		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
92	Oct. 9	Case of Joseph Y., previously studied by Dr. Howell. When prothrombin on several observations in spring of 1913 was five hours to three hours and ten minutes. For past weeks has been having kephalin by mouth. Entered hospital October 6 on account of sharp pain and swelling in groin, believed due to hemorrhage into iliac muscle. Discharged October 29 with swelling and pain gone. Up to October 17, temperature 99-100 F. Oct. 9, white blood cells, 16,680; red blood cells, 3,992,000; hemoglobin, 80 per cent. Blood smears showed diffuse basophilia of reds, slight anisocytosis, differential count normal, plates plentiful. Clot retracts well	75	2.4	80	6
92a	Oct. 15	Plates 300,000 October 15....	70	2.3	85	10

BENZOL POISONING

Case 93.—Case of severe purpura hemorrhagica due to poisoning by benzol. Entered May 2 with bleeding from gums and nose and purpuric spots all over body and retinal hemorrhages. Red blood cells, 1,460,000; hemoglobin, 25 per cent.; white blood cells, 1,500. Bleeding time fourteen and one-half minutes. Purpuric spots were first noticed about April 1.

May 3, 14, 17, 23, 31 and June 13, she received transfusions of blood; following each she improved distinctly, and the bleeding time would become two to three minutes, having been twenty-four to eight minutes before transfusion. Though improved after the transfusions, a relapse would set in with bleeding from gums and nose and fresh purpuric spots on the skin. However, after June 13 there was no more bleeding, except for a slight amount from the gums June 24 to 29. Kephalin solution applied locally to gums and also pure thrombin solution seemed to temporarily check bleeding.

The red count reached 1,971,000 with hemoglobin 48 per cent., May 17, after transfusion, and fell as low as 696,000 with 11 per cent. hemoglobin, May 31, before transfusion; reaching 1,680,000, with hemoglobin 53 per cent., June 4, and 4,528,000, with 65 per cent. hemoglobin, June 14, and July 26 3,128,000 and hemoglobin 67 per cent. In October she appeared quite healthy, with hemoglobin 80 per cent. and plates plentiful in blood smear.

Plates: Almost none seen in smears. May 9, count = 8,400; on May 31, 10,000. More plates in smears on June 2 than May 31, but distinctly scant. On July 22 they were 170,000.

TABLE 16.—Benzol Poisoning

No.	Date	Prothrombin	Antithrombin	Coagulation Time minutes	Control Prothrombin minutes
93	May 3 - Before transfusion	24	1.1	Slight + no retrac. of clot	12
93 a	May 31— Before transfusion on this day	26	—	Not done	10
93 b	June 2.....	16	—	Not done	8
93 c	July 22	12	—	Not done	8

SOME CLINICAL, PHYSIOLOGIC AND CHEMICAL OBSERVATIONS ON PTOMAIN POISONING FROM "CREAMED" CODFISH *

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AND
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On April 24, 1915, about eighty patients in the general wards and a number of the help in the kitchens of Lakeside Hospital were seized with alarming gastro-intestinal symptoms in one and a half to three hours after eating the evening meal with which had been served "creamed" codfish.[1] It was definitely ascertained that the various individuals became ill as a result of partaking of the fish. Some of the material was obtained, and it seemed worth while to make some physiologic, bacteriologic and chemical observations with it because of general medical and scientific interest in the subject of ptomain poisoning which was suspected.

Symptoms arising from "ptomain poisoning" are attributed to numerous causes. Among the more popular are: (1) gastro-enteritis due to bacterial infection; (2) effects of toxic chemical substances elaborated by bacteria, and (3) bacterial infection and toxic substances combined. Finally, there are those who place little faith in any of these explanations and prefer to disbelieve ptomain poisoning altogether. Recent investigations on a number of toxic bases which occur in and can be prepared from putrefied flesh and certain vegetable drugs, such as ergot, would seem to indicate that these might be concerned in ptomain poisoning. The effects of a number of these bases have been studied systemically and on surviving organs. An attempt was made to study the effects of our material in this direction. The chemical identification of the active substances is difficult, but the properties of a number of the bases are now well known. This has also been attempted in a general way with our material.

No claim to originality for either the methods or ideas here presented is made. However, the mode of treatment used, it is believed,

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* From the Medical Clinic, Lakeside Hospital, the Laboratory of Hygiene and Bacteriology, and the Pharmacological Laboratory, Western Reserve University.

1. It should be mentioned that the salted fish used for the preparation of the creamed fish for the patients had been inspected by the dietitian, as is her custom, and nothing unusual was found, either in appearance or in odor.

has not made a conspicuous inroad into clinical medical literature in the study of cases of ptomain poisoning. Those who are unfamiliar with the more recent aspects of the general subject of the physiologically active bases will find a clear and concise presentation of the subject in a recent monograph by Barger,[2] and in a work on toxicology by Gadamer.[3]

I. Onset and Symptoms

BY M. A. BLANKENHORN

The following report is based on the personal observation of sixteen cases in one ward of the hospital. The remaining cases were distributed among other wards and the kitchens, and the reported observations on these differed in no respect from the account given here. In all, eighty individuals were seized with sudden and alarming symptoms of distress in the gastro-intestinal tract. Many of the patients volunteered the information that they were poisoned by the fish which was served with their meal, and it was evident that the symptoms were confined to those who had eaten the "creamed" fish, and that none who had eaten it escaped. The relief of so large a number of patients demanded so great and rapid attention that detailed observations in many of the cases could not be made. However, a sufficiently large number was studied to justify the following descriptive summary:

The symptoms appeared in about one and a half to three hours after the food was taken. The most marked symptom was vomiting. This occurred in every case, usually being sudden and very severe, preceded by a "burning" in the epigastrium, and much nausea, and accompanied by exhaustion, varying from slight discomfort to a semicoma, lasting from two to five hours. The vomiting apparently bore no relation to the amount or quality of stomach content, for in some cases there was a large amount of macerated food ejected, and in others variable amounts of a clear, watery secretion. In many cases the vomiting persisted long after the stomach had been emptied. In all cases the vomitus was described as very sour and "burning." In several cases the acidity of the stomach contents was titrated with the following results: One hundred c.c. became neutral to phenolphthalein with 20 c.c. of tenth-normal sodium hydroxid; only a trace of free hydrochloric acid was present, and there was no lactic acid.

2. Barger: The Simpler Natural Bases, London, Longmans, Green & Co., 1914.

3. Gadamer: Lehrbuch der chemischen Toxikologie, Göttingen, Vandenhoeck and Ruprecht, 1909.

Eleven out of sixteen patients vomited material which resembled blood, varying from just a visible trace of pink to dark red with masses resembling clots. No chemical tests for blood were made.

From one-half to two hours after the onset of vomiting there was intestinal colic and diarrhea, in some cases very slight, in others amounting to continuous purging for several hours. There were no evidences of fever, edema or skin disturbance.

Very little treatment could be instituted. Emetics and lavage with large quantities of water were administered to those who seemed to have difficulty in emptying the stomach. In a few cases castor oil or Epsom salt was introduced into the stomach after lavage.

All the patients were fairly comfortable at the end of from twelve to twenty-four hours, except for a feeling of exhaustion and a loss of appetite. Practically all had recovered by the next day. Very sick patients had not received the fish food, and there were apparently no lasting consequences in those who ate it.

II. Bacteriologic Examination

BY G. E. HARMON

The object of this examination was to ascertain if any organisms could be isolated from the "creamed" codfish which might have been concerned in forming toxins or poisons responsible for the symptoms observed in the patients. The usual routine procedures were used. The material was plated and grown anaerobically and aerobically.

No strictly anaerobic organisms were isolated. Those which were isolated by anaerobic methods could be grown in the presence of oxygen.

Numerous varieties of cocci were isolated. In view of the fact that cocci are thought not to be actively concerned in the production of putrefactive changes, no attempt was made to identify them definitely. Most of them were varieties of staphylococcus.

Four different kinds of bacilli were found and studied. Three of these were not identified, since a preliminary study of their characteristics showed them to be saprophytes, which did not produce gas in dextrose. This would exclude *Bacillus coli communis*. Presumably no other organisms were connected with the production of substances which would explain the symptoms in the cases reported. The fourth bacillus had the following characteristics: It was motile; gelatin was not liquefied; it was negative to Gram's stain; gas was produced in lactose, dextrose and saccharose broth, and litmus milk was acidified and coagulated. These characteristics serve to identify this organism as the *Bacillus coli communior*. No other important organisms were found.

III. Physiological and Chemical Observations

BY P. J. HANZLIK

Some of the "creamed" codfish as served to the patients was procured from the hospital dietitian[4] and various extracts made from it. These were then utilized in the physiologic and chemical observations to be described. These observations were controlled with extracts made from codfish (fresh and putrefied), salted codfish (fresh and putrefied) and both these varieties "creamed" and prepared in exactly the same way as the "creamed" fish which was served to the patients.

The "creamed" fish is prepared in the hospital as follows: The salted fish are macerated in water for twelve hours. The watery extract is then discarded and the fish is steamed. Then it is removed from the steamer and creamed with a mixture consisting of flour, butter and milk, and served in about one hour. In the meantime the prepared material is kept lukewarm within the steamer.

The preparation of the extracts of the "creamed" fish from the hospital, and the physiologic effects of these will be described first. Then the results of the control material will be presented, and finally, the chemical observations.

1. PREPARATION OF EXTRACTS

The extracts of the "creamed" fish were prepared as follows, using in each case 100 gm. of the material, so that 1 c.c. of the finished product represented 1 gm. of the material:

A. The material was minced and macerated with distilled water and slightly acidified with hydrochloric acid. This was allowed to stand over night, then filtered and the filtrate made up to 100 c.c. The excess of acid in the finished extract was removed by the addition of sodium hydroxid, leaving a slightly acid reaction to litmus as it was feared that important constituents might be lost by precipitation.

B. The minced material was made moderately acid with hydrochloric acid and boiled with distilled water for two hours. Then it was filtered and the filtrate was made up to 100 c.c. The excess of acid was again removed, leaving the finished extract slightly acid to litmus.

C. The minced material was extracted with 98 per cent. alcohol over night. Then the extract was filtered and the filtrate made up to 100 c.c. Before using, the alcohol was removed by evaporation on the water bath and the residue was dissolved in water.

These extracts were now used in the physiologic observations to follow.

4. Thanks are due to Miss Graves, chief dietitian at Lakeside Hospital, for her kind cooperation in this investigation, and to Mr. Beebower, supply agent, who secured the material. Inasmuch as the dietitian discovered no apparent putrefaction in the fish when it was used, it is probable that the spoiling must have occurred before the fish was salted, and that the evidences of putrefaction were masked by the salting.

2. PHYSIOLOGIC EFFECTS

Surviving Intestine.—Longitudinal and circular strips of cat's and rabbit's intestine were suspended in oxygenated Tyrode's solution, and their spontaneous movements were recorded on a slow moving drum by a weighted lever in the usual manner. The results obtained are briefly summarized in Table 1. Figures 1 and 2 will serve to illustrate some of the typical effects obtained.

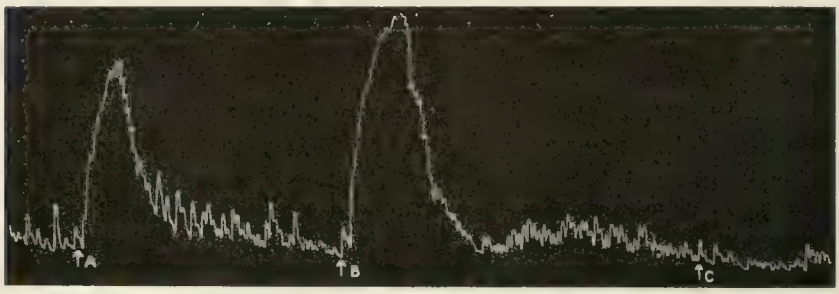

Fig. 1.—Effect of extracts of "creamed" fish (hospital material) on longitudinal strip of surviving cat's intestine. Tyrode solution at 37.5 C. *A*, 1 c.c. of Extract A (alkaline); *B*, 1 c.c. of Extract A (slightly acid); *C*, 2 c.c. of Extract B.

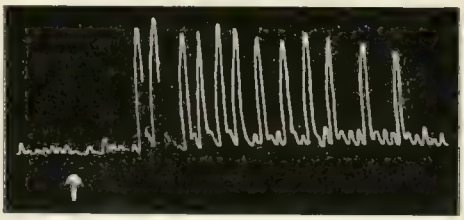

Fig. 2.—Effect of alcoholic extract of "creamed" fish (hospital material) on longitudinal strip of surviving cat's intestine. At point marked by arrow, 1 c.c. of Extract C.

TABLE 1.—EFFECTS OF EXTRACTS OF "CREAMED" FISH ON SURVIVING INTESTINE

Extract *	Description of Peristalsis
A	Marked increase in tone; rate and amplitude only in some cases moderately increased. Same effects observed when extract was made alkaline.
B	No increase in tone, rate or amplitude.
C	Very slight increase in tone; in some cases marked increase in amplitude; rate unchanged.

* One c.c. of the extract was usually added directly to the organ in 100 c.c. of Tyrode.

These show a stimulation of peristalsis with marked increase in tone and some increases in amplitude and rate, with the aqueous acid extract (A) of the "creamed" fish. The effects are not due to the acid reaction, as they took place equally readily when the extract was made alkaline or neutralized. The aqueous acid extract made by heat had no effect. The alcohol extract produced only an increase in the

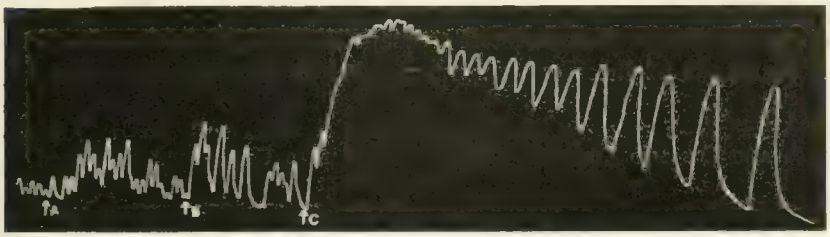

Fig. 3.—Effects of extracts of "creamed" putrefied codfish and "creamed" putrefied salted codfish (controls) on longitudinal strip of surviving cat's intestine. *A*, 2 c.c. of Extract I; *B*, 2 c.c. of Extract I; *C*, 2 c.c. of Extract J (creamed putrefied salted codfish).

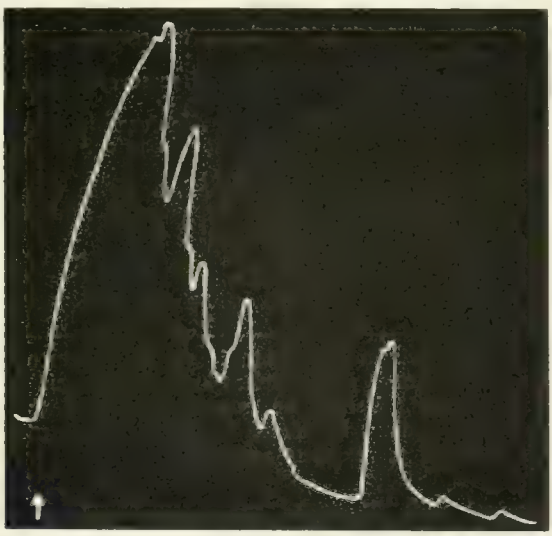

Fig. 4.—Effect of extract of "creamed" putrefied salted codfish (control) on strip of surviving pregnant uterus of guinea-pig. No spontaneous contractions for an hour before extract was applied. Arrow, 1 c.c. of Extract J.

amplitude of peristalsis. The augmentor effects produced by the aqueous acid extract closely resemble those of histamin. Putrescin and cadaverin are said to produce analogous effects, though not so pronounced.

When it was ascertained that only the aqueous acid extract made in the cold gave the most constant and maximal effects, the extracts of the control material were made in this way. The control experiments were made in order to ascertain if physiologically active extracts required putrefied material, and whether or not the process used in the preparation of the "creamed" fish gave the optimal conditions. It was found to be true that only salted codfish when first allowed to putrefy and then was "creamed" and prepared according to the hospital method gave the most constant and typical physiologic effects. The results of these experiments are briefly summarized in Table 2;

TABLE 2.—Effects of Extracts of Fresh, "Creamed" Fresh, Putrefied and Creamed Putrefied Codfish and Salted Codfish on Surviving Intestine

Designation of Extract	Description of Extract *	Description of Peristalsis
D	Fresh codfish	No effect after several applications of 2 c.c.
E	Fresh salted codfish	No effect after several applications of 2 c.c.
F	"Creamed" fresh codfish	No effect after several applications of 2 c.c.
G	"Creamed" fresh salted codfish	No effect after several applications of 2 c.c.
H	Putrefied codfish	Very slight increase in amplitude and tone; diminution in rate with single applications of 2 c.c.
I	"Creamed" putrefied codfish	Very slight increase in tone and amplitude; somewhat more in rate after single applications of 2 c.c.
J	"Creamed" putrefied salted codfish	Very marked increase in tone which was lasting; marked increase in amplitude during relaxation; rate unchanged generally.

* One c.c. of each extract represents 1 gm. of the material, which was macerated with distilled water and sufficient hydrochloric acid to give a moderately strong acid reaction. Before the extracts were used, the excess of acid was neutralized with sodium hydroxid, leaving a faint trace of acidity to litmus. Usually 2 c.c. of the extracts were used.

Figures 3 and 4 will illustrate the typical effects obtained, and Figure 5 the effects of epinephrin, atropin and papaverin on intestine treated with the active extract.

The results indicate that only the aqueous acid extract of the "creamed" putrefied salted codfish gave typical effects, and that these were practically identical with the effects obtained with the hospital material. Extracts from plain and "creamed" fresh or putrefied codfish and "creamed" fresh salted fish produced practically no effects. It is clear that putrefaction of the fish is essential for the production

of the augmentor effects on peristalsis. It seems also to be necessary to "cream" and prepare the fish as was done for the patients. This mode of preparation may establish some suitable condition under which liberation of the active chemical substances takes place. It will be shown later that apparently a certain bacterial environment is also necessary to produce physiologically active culture mediums.

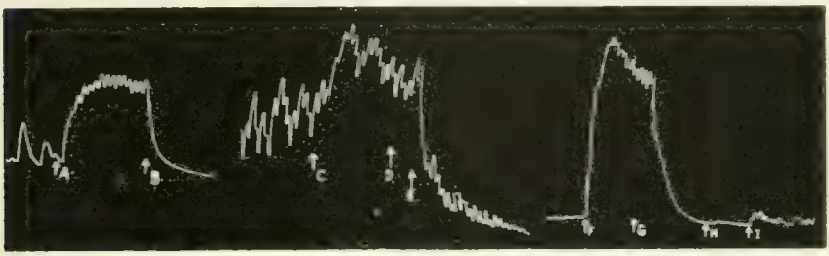

Fig. 5.—Effects of epinephrin, atropin and papaverin on surviving cat's intestine treated with extract of "creamed" putrefied salted codfish. *A*, 1 c.c. of Extract J; *B*, 0.2 c.c. of epinephrin, 1:1,000; *C*, 1 c.c. of Extract J; *D*, 0.2 cc. of papaverin hydrochlorid; *E*, 0.2 c.c. of papaverin hydochlorid, 1:1,000; *F*, 1 c.c. of Extract J; *G*, 0.1 c.c. of atropin sulphate, 1 per cent.; *H*, 1 c.c. of Extract J; *I*, 1 c.c. of Extract J.

Fig. 6.—Effect of acid extract of "creamed" putrefied salted codfish on systemic blood pressure (dog, 5.6 kg). At arrow, 1 c.c. of Extract J per kilogram intravenously.

Surviving Uterus.—The effects produced were essentially similar to those on the intestine, namely, a marked stimulation of peristalsis. Figure 4 illustrates a typical reaction with the aqueous acid extract of putrefied "creamed" codfish.

Blood Pressure.—The various extracts were injected intravenously into dogs, and the blood pressure was recorded by a dampened mercury

manometer in the usual manner. The dosage varied from 1 to 2 c.c. per kilogram. All of the extracts from the hospital material and the controls produced a fall in blood pressure followed by a rise, except the aqueous acid extract (A) of "creamed" putrefied salted codfish, in which the fall was not followed by a rise in pressure, but rather a slow tendency to recovery. This result was constant, and resembles the characteristic effects obtained with histamin. The initial rapid fall is presumably of endocardial origin. A pressor effect in the same animal was obtained after the injection of epinephrin, showing that the mechanism by which this is brought about was functionally active. The fall in pressure could not be due to albumoses or peptone because some of the other extracts which contained these substances did not give the typical effect of Extract A. On the contrary, a slight rise in pressure was usually obtained after the primary fall. Figure 6 illustrates a typical blood-pressure effect.

3. EFFECT OF BACTERIAL CULTURES OF "CREAMED" FISH ON SURVIVING INTESTINE

The various culture mediums which were incubated with the hospital material by Dr. Harmon were applied directly to strips of surviving intestine. The object of this was to ascertain roughly, if possible, the kind of environment (as judged by mediums of different

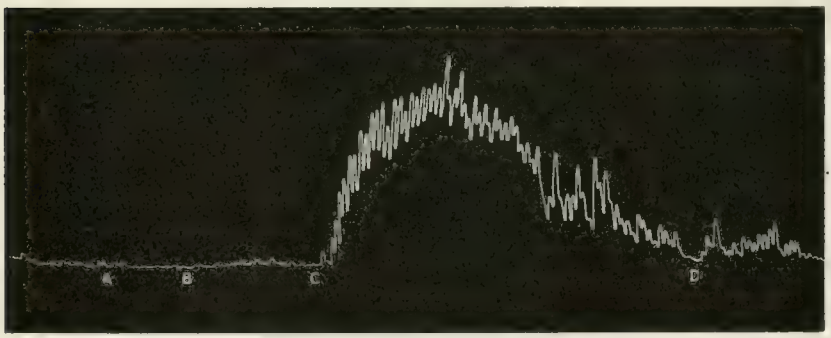

Fig. 7.—Effects of culture mediums incubated with "creamed" fish on surviving cat's intestine. *A*, 2 c.c. of bouillon culture of fish food; *B*, 2 c.c. of lacmus milk culture of fish food; *C*, 2 c.c. of bouillon dextrose culture of fish food; *D*, 0.5 c.c. of 10 per cent. sugar.

composition) that is most favorable to the organisms for the development of the physiologically active toxic substances. It was interesting to find that only one culture, namely, bouillon-dextrose, out of several that were used, produced a physiologic response, and this resembles essentially the effects produced by the aqueous extract (A) of the hospital material itself. The effects of plain bouillon and dextrose

alone were excluded because no effects were produced by the inoculated mediums. The effects of the various cultures are briefly summarized in Table 3 and illustrated by Figure 7.

TABLE 3.—Effects of Cultures Incubated with "Creamed" Fish on Surviving Intestine

Culture Medium and Quantity Used	Description of Peristalsis
Plain bouillon, 2 c.c.....	No effect on tone, rate or amplitude.
Lacmus milk, 2 c.c.....	No effect on tone, rate or amplitude.
Emulsion from agar stab, 2 c.c.	No effect on tone, rate or amplitude.
Bouillon-dextrose, 2 c.c...	Marked increase in tone; some increase in rate; no increase in amplitude.
Dextrose 10%, 2 c.c.....	No effect on peristalsis.
Extract A (fish).....	Marked increase in tone; some increase in rate and amplitude. Effect removed by 0.2 c.c. papaverin HCl 0.1 per cent.

4. CHEMICAL OBSERVATIONS

The general principles recommended in Barger's monograph for the extraction and purification of the simpler bases were followed. As no more of the hospital material was available, the "creamed" putrefied salted codfish used in the control experiments, which behaved similarly physiologically, was used. No attempt was made to isolate the active chemical substance or substances in the form of pure salts as the technic is beset with numerous difficulties and would require more time than was justified in spending. As pure an extract was obtained as possible which would permit the application of certain of the group reactions for the supposed bases and other products.

An aqueous acid extract in the cold of the "creamed" putrefied salted codfish was made by treating about 200 gm. of the macerated material with hydrochloric acid. The material was thoroughly expressed and the liquid extract evaporated and dried in vacuum. It was necessary to eliminate the use of heat, since it was found that an extract obtained by heat was physiologically inactive, and it is known that many of the bases are destroyed by heat. The thick smeary residue was then treated with 95 per cent. alcohol to remove as much protein and other precipitable materials as possible. Enough water was present under these conditions to retain the active bases in solution. The alcohol was removed by spontaneous evaporation at first, and finally, in vacuum. The residue now remaining was treated with water, and appeared to dissolve completely with some opacity. This was then treated with both the basic and ordinary lead

acetate three times, the lead being removed each time by precipitation with hydrogen sulphid. Finally, when all the lead was removed, the remaining extract, which appeared to have a slightly yellowish tint, was treated with animal charcoal in the cold and filtered. The filtrate appeared entirely colorless and transparent. This filtrate was then used for the various tests as follows:

1. Pauly's reaction[5] with p-diazobenzene sulphonate gave a yellowish with rose-pink at first and finally a deep orange. This was controlled with a very dilute solution of histamin, which gave a similar set of colors, namely, yellow with rose-pink at first and finally a deep orange. A strong histamin solution gave colors which were more intense. The reagent alone gave a very light yellow which did not develop as rapidly as with the filtrate or histamin, and showed no rose-pink or deep orange. Dialyzed egg-albumin gave the same as the reagent alone, but a weak peptone solution gave colors very similar to those of the extract and histamin.

2. The fish extract did not give a positive biuret test. This would exclude protein, such products as peptone and also histidin.

3. Knoop's test (boiling with bromin water) was not positive. This would also exclude histidin.

The results obtained with these tests roughly indicate that the general group of diamins is concerned. To this group belong histamin, putrescin and cadaverin. It is not maintained that the presence of either one or all of these products is demonstrated. However, other substances which are said to give Pauly's reaction, such as alcohol, chrysarobin, creosote, cresols, dionin, guaiacol, heroin, morphin, naphthol, opium, phenol, tannic acid, etc.,[6] do not come into consideration here; purins and other analogous products which occur in normal urine (also positive with Pauly's reagent, though not characteristically), and also tyramin, are excluded because these do not give any known physiologic reactions such as were obtained with extracts of the fish material, or clinical symptoms as exhibited by the patients.

IV. Comment

BY P. J. HANZLIK

From the nature of the clinical evidence obtained, it appears that the symptomatic attack which seized the patients was not of bacterial origin. The attacks took place within three hours, which is much

5. The reagents used in this reaction are: (1) 0.5 per cent. solution of sodium nitrite, and (2) 0.5 per cent. solution of sodium sulphanilate. The reagents are used in the proportion of 1 of the nitrite to 50 of the sulphanilate, and are not mixed until the test is to be made.

6. Hawk: Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1913, p. 360.

shorter than the incubation period of any known organism. It appears, then, that some other cause was present. This might be chemical, that is, some chemical substance, which was already present in the fish food before it was ingested. The origin of this, in turn, might be bacterial or autolytic. It is presumed that it was bacterial. The rapidity, violence and suddenness of the attacks would indicate some active chemical substance which was preformed and readily absorbed.

Physiologically, it can be said that the experiments on surviving organs indicate that some substance markedly stimulating to peristalsis was present in the material. The tone of both intestinal and uterine musculature was markedly increased. In fact, this seemed to be the most striking effect. However, the rate and amplitude of the intestinal peristalsis were also increased at times. These reactions would not necessarily explain the gastro-intestinal symptoms observed in the patients, but it is suggestive. Increased peristalsis of the intact intestine was observed in a dog which had received an intravenous injection of the most active fish extract (A). These effects are quite analogous to those obtained with histamin and similar diamins, such as putrescin and cadaverin, which can be prepared from decomposed flesh. The effect on the systemic blood pressure resembled that of histamin, namely, a fall with a gradual tendency to recovery. These reactions cannot be attributed to protein or its decomposition products, such as albumoses and peptones, or even purins, because many of these are not known to have any such physiologic effects, and moreover, certain of the extracts which contained these products produced no effects. It would appear that these physiologic actions are due to some chemical substance which is elaborated under certain favorable conditions, namely, from salted codfish which is previously allowed to putrefy and then is "creamed" and prepared as described in the text. An aqueous acid (hydrochloric acid) extract of such fish food gave the most marked and constant typical effects. A similar extraction could conceivably occur in the stomach, that is, by the solvent and digestive power of the gastric juice. The alkalinity of the intestine would not remove the physiologic effects, as no interference with the typical intestinal reaction was observed when the active acid extract was rendered alkaline.

The chemical evidence is incomplete. However, it may be stated that the physiologically active substance is destroyed by prolonged boiling, as the boiled extracts were inactive. Alcohol does not remove it completely. An aqueous acid (hydrochloric acid) extract in the cold was the most active and gave constant results. (Only the "creamed" putrefied salted codfish is here referred to, as the fresh fish and salt fish under other conditions gave inactive extracts.) The

fact that Pauly's reaction with p-diazobenzene sulphonate was positive in the absence of protein (excluded by purification and negative biuret reaction) seems to indicate that some base belonging to the general group of diamins represented by such products as histamin, putrescin and cadaverin derived from putrefied flesh is present. The presence of purins and other analogous substances is excluded by the nature of the symptoms and the physiologic effects on blood pressure and surviving organs.

V. Conclusions

1. The clinical symptoms observed in a large number of patients attacked with ptomain poisoning from "creamed" salted codfish were epigastric distress, nausea, vomiting, intestinal colic and diarrhea. Complete recovery occurred in from twelve to twenty-four hours, in a part of the individuals spontaneously, and in another part following gastric lavage.

2. Bacteriologic examination of the "creamed" fish showed the presence of the *Bacillus coli communior,* and other saprophytes and some staphylococci.

3. The gastro-intestinal disturbances are not attributed to infection by the organisms in the fish material.

4. Extracts of the "creamed" fish gave practically the same physiologic reactions as the same brand of salted codfish which was previously allowed to putrefy and then was prepared in the same manner as the food served to the patients.

5. The physiologic effects consisted of a marked stimulation of intestinal and uterine peristalsis with surviving organs, and a fall of blood pressure with gradual recovery.

6. The purified active extract of the "creamed" putrefied salted codfish contained some physiologically active base, whose chemical reactions resemble those of the group of diamins to which putrescin, cadaverin and histamin belong.

OBSERVATIONS ON SINO-AURICULAR HEART BLOCK *

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Heart block is ordinarily understood to be a condition in which there is impairment in the conduction of impulses from auricles to ventricles. The first stage of this process is represented by a mere delay in the conduction time recognized by an increase in the a-c interval in jugular tracings and in the P-R time in electrocardiograms. In this condition all impulses reach the ventricle; but if the delay is sufficient or if the heart rate is rapid, an impulse may occasionally fail to reach the ventricle, giving partial heart block. Finally, there is a condition in which none of the auricular impulses reach the ventricle, and the auricles and ventricles each beat of their own rhythm and independently of one another. These three stages may be termed, first, *delayed conduction,* second, *partial heart block,* and third, *complete heart block.* The cause of this disturbance in heart mechanism lies in the effect of some toxin or some degenerative change on the auriculoventricular node of Tawara or on the main stem of the bundle of His. Any of the three stages may result from the action of digitalis, from acute febrile conditions, particularly rheumatic fever, and from chronic degenerative processes involving the conductive mechanism of the heart, such as cardiac sclerosis or gummas.

It might be expected that changes similar to those which occur in the auriculo-ventricular node and bundle of His would take place when similar abnormal conditions existed in the vicinity of the sino-auricular node, which has much the same function and structure as the auriculoventricular node. One is, in fact, surprised that defective conduction between the sinus node and auricle is so rarely observed. As at present there is no simple means of determining a sino-auricular (S-A) interval corresponding to the auriculoventricular interval (a-c or P-R), delayed conduction in this region, if it occurs, cannot be recognized. It follows that not all conditions in which the first stage of block might exist are recognized as such, for the S-A interval may be much prolonged without causing any change detectable by any of the graphic methods of heart diagnosis. However, if the second stage of block is

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present, then the condition can be recognized either by jugular tracings or more accurately by electrocardiograms, for a complete heart cycle is dropped and the pause is approximately twice the length of the normal heart cycle. Four such cases observed by the author in the medical clinic of the Peter Bent Brigham Hospital are here reported with a historical review of the subject, and certain observations on the condition.

HISTORICAL REVIEW

In 1883 Gaskell[1] showed that the *primum movens* in the tortoise's heart was located near the mouth of the great veins. Between that time and 1907, when Keith and Flack[2] made the discovery that histologically there could be seen a specialized tissue in this vicinity, many investigators have published results similar to Gaskell's, working with various cold and warm blooded animals. It has long been known that the automaticity and the rhythmicity of the heart musculature diminishes from above downward, that is, under normal conditions the sinus region is most automatic, and in lesser degree the auricles and ventricles, respectively. This explains to some extent why the cardiac impulse and contraction first appears in the region of the great vessels and spreads downward. It has always been a debatable question, however, whether the activity in the sinus region produces any noticeable effect either in animals or in the human being. Is there a real sinus wave in the normal jugular curve due to the contraction of the superior vena cava? Hering[3] in 1900, experimenting on dogs and rabbits, brought out the contraction of the big veins by cooling the sinus region, thereby slowing the rate of the heart. He said:

> The slower the heart action now becomes, the more plainly one may see that unquestionably the pulsation of the veins precede that of the auricles. Furthermore, one can see that only after several pulsations of the vein does an auricular contraction follow. Finally, the veins pulsate very feebly without being followed by any auricular contraction.[4]

Erlanger,[5] in his exhaustive study of heart block, suggests that a positive wave in the neck before the auricular systole, in a case which

1. Gaskell, W. H.: On the Innervation of the Heart, with Especial Reference to the Heart of the Tortoise, Jour. Physiol., 1883, iv, 43.

2. Keith, A., and Flack M.: The Form and Nature of the Muscular Connections Between the Primary Divisions of the Vertebrate Heart, Jour. Anat. and Physiol., 1907, xli, 172.

3. Hering, H. E.: Zur experimentellen Analyse der Unregelmässigkeiten des Herzschlages, Arch. f. d. ges. Physiol., 1900, lxxxii, 1.

4. Je langsamer nun die Herzaction wird desto deutlicher sieht man dass ganz unzweifelhaft den Pulsationen der Venen, jene der Vorhofe folgen. Weiterhin kann man beobachten dass erst auf mehrere Pulsationen der Vene eine Vorhofscontraction folgt. Schliesslich pulsieren nur noch die Venen ganz schwach, ohne von Vorhofschlagen gefolgt zu werden.

5. Erlanger, J.: On the Physiology of Heart Block in Mammals, with Especial Reference to the Causation of Stokes-Adams' Disease, Jour. Exper. Med., 1905, vii, 676.

had complete heart block and which therefore permitted the auricular waves to appear distinctly during the long ventricular pauses, may be due to the contraction of the great veins. The curves of this case are quite clear, but there is a considerable interval between these sinus waves and the auricular waves, which is contrary to the work recently reported by Eyster and Meek.[6] These authors have shown that the impulse travels from the pace maker at the head of the sinus node upward to the superior vena cava quite rapidly, and to the auricular musculature more slowly; but the difference in speed is not greater than 0.02 second. Considering that conduction is less rapid in the human heart, it is still much too short a time to permit any distinct wave to appear.

It may well be that a sinus wave appears distinctly in the jugular curves only under the most favorable circumstances. The proper venous pressure may be necessary. Or if there is a delay in the conduction of the impulse from sinus region to the auricles, a small wave due to the contraction of the mouth of the superior vena cava might appear which otherwise would have been lost in the auricular wave. These several factors may account for the failure in most instances to obtain such a wave either in animals or in man. The same uncertainty exists in electrocardiography. It is thought by some investigators that a split "P" wave does not necessarily represent the retarded contraction of one or the other auricle, but that it is due to sinus activity. Hering,[7] by vagal stimulation in dogs, caused a small wave to appear 0.02 second before the "P" wave in electrocardiograms. Von Hoesslin[8] found that the "P" waves became notched during vagal pressure in man, but that the notch came after the point where the auricular complex started, that is, between the P and R waves. One must distinguish in this connection between a possible pressure wave as a result of the contraction of the superior vena cava and a wave in the electrocardiogram as a result of sinus activity. They have both been called sinus waves, but their causes and their time relations are different. The latter must necessarily come before the main auricular complex, while the occurrence of the former will depend on the relative speed with which the impulse reaches the veins and the auricles. Kahn[9] found a notch in the P wave of horses which would come 0.04 second after the beginning of the auricular complex, but in some cases the

6. Eyster, J. A. E., and Meek, W. J.: Experiments on the Origin and Propagation of the Impulse in the Heart, Heart, 1914, v, 119.

7. Hering, H. E.: Experimentelle Studien an Saugethieren über das Elektrokardiogramm, Arch. f. d. ges. Physiol., 1909, cxxvii, 155.

8. Von Hoesslin, H.: Beobachtungen über den Einfluss des vagus auf das menschliche Herz, Deutsch. Arch. f. klin. Med., 1914, cxiii, 537.

9. Kahn, R. H.: Das Pferde-Ekg, Arch. f. d. ges. physiol., 1913, cliv, 1.

second portion of the curve would be smaller than the first. On measuring back from the first point of the mechanical curves traced by the auricular contraction, and assuming that the time from the electrical to the mechanical evidence of contraction is the same for auricle and ventricle, he found that the first part of the wave corresponded to auricular contraction. It is difficult, therefore, to explain a notching which occurs after the auricular complex has begun, as due to activity in the pace maker which is first to become electrically negative. Weil,[10] in a recent publication, states that the notching of the P wave is due to delayed conduction in the sinus node, or between the node and the auricles and that the first part is a result of sinus activity. According to Norr,[11] in the electrocardiogram of some horses a distinct wave is seen 0.08 second before the auricular wave, which he thought was due to the contraction of the great veins. One can readily see from this brief résumé that the question of sinus waves is unsettled and problematic.

It is not necessary that there should be an evident wave in the electrocardiogram as a result of sinus activity in order to draw conclusions as to physiologic and pathologic processes going on in the S-A node. It has been shown by Lewis, Oppenheimer and Oppenheimer[12] that over the specialized tissue described by Keith and Flack there is a point on the sulcus terminalis and in the immediate neighborhood of its upper extremity, close to the cavo-auricular angle, which becomes electrically negative before any other part of the auricular musculature. Eyster and Meek,[6] using the same index, determined the course of the impulse in the mammalian heart by placing two electrodes on various portions of the auricles. They found that the impulse started at the upper end of the node and traveled most rapidly to the mouth of the superior vena cava and less rapidly to the lower part of the node itself. According to their calculations, it took 0.01 second to reach the lower part of the node, but a shorter time was required to reach the superior vena cava, while to a point on the right auricle only 2 or 3 mm. away from the node, the duration was from "0.015 to 0.025" second.

Blocking of impulses at the pace maker was observed experimentally by Hering[3] in 1900, and later[13] in 1906 he obtained pauses of the auricles and ventricles approximately twice the normal length by

10. Weil, A.: Beiträge zur klinischen Elektrokardiographie, Deutsch. Arch. f. klin. Med., 1914, cxvi, 486.

11. Norr, J.: Das Elektrokardiogramm des Pferdes. Seine Aufnahme und Form, Ztschr. f. Biol, 1913, lxi, 197.

12. Lewis, T., Oppenheimer, B. S., and Oppenheimer, A.: The Site of Origin of the Mammalian Heart Beat, Heart, 1910-1911, ii, 147.

13. Hering, H. E.: Ueberleitunzsstörungen am Saugethierherzen mit zeitweiligen Vorhofsystolenausfall, Ztschr. f. exper. Path. u. Therap., 1906, iii, 511.

clamping the A-V node. Erlanger and Blackman[14] were able to make the veins of the rabbit beat twice as fast as the auricles by passing a thread down the superior vena cava and out through the inferior cava and twisting the thread, the torsion causing pressure on the S-A node. In a later publication, Erlanger[15] thought that in similar experiments when the auricles were beating regularly and slowly there was complete sino-auricular dissociation. In studying the effect of aconite on dogs, Cushny[16] noticed sudden halvings of the auricular and ventricular rate, which he thought was due to a blocking of every other impulse at the sinus node.

REVIEW OF CLINICAL CASES OF SINO-AURICULAR BLOCK

From a clinical standpoint, occasional cases showing sino-auricular block have been reported. In 1902 Mackenzie[17] discussed a case and showed radial and jugular tracings in which there were pauses approximately twice the normal heart cycle. During some of these pauses an "a" wave appeared in the jugular, while during others no wave was present. He did not say that the failure of the auricles to contract was due to a S-A block, but it seems quite possible from his tracings that there was block present in both nodes. Joachim[18] reported four cases of heart block with radial tracings of two and both radial and jugular tracings of the other two. The pauses in the radial tracings were more or less short of being twice the length of the normal cycle. The "a" waves were absent in the jugular curves during the pauses. In three of these cases the cycle after the pause was generally longer than the other normal cycles. (Reference to this point will be made later in connection with the cases observed by the author.)

Wenckebach[19] discussed two cases of heart block showing jugular and radial tracings. The first one was a young man in good health who showed a gradual increase in the a-c interval until an "a" wave appeared in the neck which was not followed by a ventricular beat. Following this pause, however, neither auricle nor ventricle contracted, which signified that the impulse was blocked at the S-A node. The

14. Erlanger, J., and Blackman, J. R.: A Study of Relative Rhythmicity and Conductivity in Various Regions of the Auricles of the Mammalian Heart, Am. Jour. Physiol., 1907, xix, 125.

15. Erlanger, J.: Irregularities of the Heart Resulting from Disturbed Conductivity, Am. Jour. Med. Sc., 1908, cxxxv, 797.

16. Cushny, A. R.: The Irregularities of the Mammalian Heart Observed under Aconite and on Electrical Stimulation, Heart, 1909, i, 1.

17. Mackenzie, J.: The Cause of Heart Irregularities in Influenza, Brit. Med. Jour., 1902, ii, 1411.

18. Joachim, G.: Vier Fälle von Störung des Reizleitung im Herzmuskel, Deutsch. Arch. f. klin. Med., 1905, lxxxv, 373.

19. Wenckebach, K. F.: Beiträge zur Kenntnis der Menschlichen Herztätigkeit, Arch. f. Anat. u. Physiol., Physiol. Abt., 1906, p. 297.

second case was one of hypertension with an intermittent pulse, the pauses being twice the normal heart cycles. The a-c interval was at no time increased, and in all but two occasions "a" waves appeared in the jugular. The failure of the auricles to contract on these two occasions he thought was due to insufficient irritability of the auricles. Hewlett,[20] in 1907, reported a case which showed ordinary a-v block with occasional instances in which the auricles as well as the ventricles were blocked. The pauses in the latter instances were almost equal to two heart cycles. There was also present a slight sinus arrhythmia.

In the case reported by Gibson[21] the patient had a history of syphilis, acute rheumatic fever and excessive use of alcohol; hypertension was present. Polygraphic tracings showed that the a-c interval was 0.7 second and that every other ventricular beat was blocked. A small wave which appeared 0.7 second before the "a" wave was thought to be due to contraction of the superior vena cava. This very long S-A interval must be accepted with some doubt, although it did diminish to 0.4 second eleven minutes after an atropin injection.

Rihl[22] reported a rather doubtful case with radial and jugular tracings in which there were pauses a little less than twice the length of one heart cycle, some having "a" waves and others not. The patient had been on digitalis at the time. A very striking instance of prolonged arrest of all chambers of the heart was reported by Laslett[23] in which the patient had attacks of faintness during the long pauses. The periods of inhibition do not measure out to be multiples of the normal heart cycle, and so it is questionable whether impulses were really blocked or whether it was a vagus slowing of the pace maker itself. The fact that excitement and exertion made these pauses disappear is in favor of the latter. In a more recent contribution by Riebold,[24] although no tracings were given, numerous interesting figures of the heart rate appeared. A young man quite sick with typhoid had a pulse rate of 120. A few days later the pulse was coupled at the rate of 80, and then it became regular at the rate of 40. At other times it was noticed to be regular with a rate of 60. Digitalis had been given, and because these figures are all simple fractions of the original

20. Hewlett, A. W.: Digitalis Heart Block, Jour. Am. Med. Assn., 1907, xlviii, 47.

21. Gibson, G. A.: Further Observations on Heart Block, Practitioner, London, 1907, p. 589.

22. Rihl, J.: Klinischer Beitrag zur Kenntnis der Ueberleitungsstörungen von der Bildungsstatte der Ursprungsreize zum Vorhof, Deutsch. Arch. f. klin. Med., 1908, cxiv, 286.

23. Laslett, E. E.: Syncopal Attacks Associated with Prolonged Arrest of the Whole Heart, Quart. Jour. Med., 1908-1909, ii, 347.

24. Riebold, G.: Reizleitunzstörungen zwischen der Bildungsstatte der Ursprungsreize der Herzkontraktronen in Sinus der Oberen Hohlvene und dem Vorhof (sino-auricularer Herzblock), Ztschr. f. klin. Med., 1911, lxxiii, 1.

pulse rate 120, it was thought that at first all sinus beats came through and later every third, then every second, or two of every three beats were blocked at the S-A node. It is surprising to note, if this be true, that the sinus rate remained constantly at 120 during the entire time. There was given no reliable evidence that the block did not take place at the a-c node. In the second case reported by the same author, after a third injection of 1 drop of tincture of strophanthus, the pulse fell from 102 to 51, and during the next few days was counted at 34, 25, 20 and 17, namely, one-half, one-third, one-fourth, one-fifth and one-sixth of the original rate of 102. It is fair to say that during such long pauses it ought to be less difficult than usual to hear the auricular contractions, and to see the auricular waves in the jugular vein. No such signs were made out here. It was therefore concluded that varying degrees of block were present at the S-A node.

An electrocardiographic study of a case of acute rheumatic fever by Schott[25] describes a condition of paroxysmal tachycardia with a regular rate of 200 coming after the patient had been fever-free for two weeks. During the tachycardia there were pauses exactly equal to two or three heart cycles, in which no waves were present at all.

In Table 1 are collected summaries of the fourteen cases of S-A block[26] which could be found in the literature, together with the four cases reported here. Only one of the cases from the literature was studied with the electrocardiograph; two were studied with radial tracings, two without any of the graphic methods, and all the rest with simultaneous jugular and radial tracings. Of these eighteen cases, ten manifested the arrhythmia only after having been given digitalis or some related body such as strophanthin; in four cases digitalis was definitely in no way related to the arrhythmia; in two nothing is said about digitalis, and in the last two, although no statement is made, the patients were suffering from cardiac decompensation and so might well have received it. Of the four cases that were not related to digitalis, one had S-A block during attacks of paroxysmal tachycardia which occurred during the convalescence from acute rheumatic fever; another was in a man who was otherwise well; the third was in a woman who had chronic cardiac trouble with attacks of syncope, and the fourth is Case 1 described below. The third case is better classified as one of vagal inhibition rather than S-A block, for the condition was not persistent and the pauses were not sufficiently approximate to

25. Schott, E.: Ueber Vorhofsystolenausfall., München. med. Wchnschr., 1912, lix, 292.

26. Since this paper was written one case of sino-auricular block in a healthy man was described by J. A. E. Eyster and J. S. Evans, The Archives Int. Med., 1915, xvi, 832. Two other electrocardiograms of S-A block were noticed in T. Lewis' "Clinical Electrocardiography," one of which resulted from digitalis therapy.

simple multiples of the length of the normal heart cycles (Laslett's case). Most of the cases showed a greater or lesser degree of sinus arrhythmia (see Table 1). The significance of this will be taken up more fully later.

Of the four cases which were studied here, the first two will be taken up in greater detail because they may serve as two different types, while the last two will be just briefly mentioned because the condition was only the incidental result of digitalis therapy.

Case 1 (Medical No. 1991).—K. S., a short stout woman, aged 56, entered the hospital, Dec. 3, 1914, complaining of a jumping heart. The patient had never been sick before. The family history was unimportant. About one month before the patient was taken ill with a severe "cold" in the head and chest and had severe diarrhea, ten movements a day. She noticed for the first time that her heart jumped. This condition lasted one week. The heart quieted down and then she was well for ten days. A similar attack in which her cardiac symptom was more prominent and her gastro-intestinal less so began two weeks ago. The diarrhea cleared up in a few days but the jumping of the heart persisted and this brought her to the hospital.

On physical examination it was found that the eyes, ears and nose were normal; teeth were in poor condition; the skin showed some dermatographia; the lungs were hyperresonant. The heart borders were very difficult to determine. The left border was about 12.5 cm. from the midline in the fifth interspace. The sounds were irregular, that is, after every third or fourth beat there was a long pause, and the systolic murmur after the long pause was slightly accentuated. During the pause no sound could be heard and no wave could be seen in the jugular vein. Sino-auricular block was present. The pulses were equal and showed the same arrhythmia as the heart sounds. The arteries were somewhat rigid and under high tension. Systolic blood pressure was 196 and diastolic 98. The abdomen and extremities were negative. The deep reflexes were present but somewhat active. The urine had a specific gravity of 1.028; there was a slight trace of albumin and no sugar. One hyaline cast was seen in five examinations. Phenolsulphonephthalein output in two hours was 41 per cent. Blood nitrogen, 23 mg. per hundred c.c. of blood. Blood Wassermann was negative. The condition of the patient remained about the same except that she gained strength so that in seventeen days she walked out of the hospital without any difficulty. Numerous electrocardiograms were taken, some simultaneously with jugular and brachial curves.

Feb. 24, 1915, the patient returned to the outdoor department complaining of constipation and bleeding hemorrhoids. At this time further electrocardiograms were taken which showed that her arrhythmia remained practically unchanged. She did quite well under medical treatment, but on April 22, 1915, she was again admitted to the wards for further study. Observations on the effect of atropin and vagal pressure were made. During this period of five months many electrocardiograms were taken, and the same condition of S-A block was always present. No digitalis was administered at any time. In July, 1915, it was learned that the patient was up and about, and doing a moderate amount of housework.

Case 2 (Medical No. 2212).—Man, aged 42, boiler-maker, entered the hospital Jan. 23, 1915, suffering from shortness of breath and swelling of the feet. His mother died of diabetes and heart trouble. There was an asthmatic history in the father's family. The patient had married twice, and both wives had many miscarriages. He had used tobacco and alcohol to excess and had always done hard muscular work under poor hygienic conditions. He had measles, diphtheria, scarlet fever, malaria, smallpox, pneumonia, gonorrhea, and three

TABLE 1.—Review of Cases

Case	Diagnosis	Sex*	Age	Blood Pressure	A-C Interval, Second	History of Rheumatic Fever	Tracings	Relation of Digitalis to Arrhythmia	Length of Consecutive Heart Cycles, Including the Blocked Beat, Second	Extreme Sinus Variations in Length of Heart Cycles, Second
Mackenzie	Influenza	♂	40		0.4	+	Jugular; radial	Not stated	0.94, 0.81, 0.84, 0.89, 1.70, 0.90, 1.79, 1.72, 0.94, 0.81	0.82 to 0.96
Joachim....	1. Cardiac decompensation	♀	73				Radial	Not stated	0.56, 0.54, 0.54, 0.56, 0.54, 1.04, 0.60, 0.56	0.54 to 0.60
	2. Mitral insufficiency; acute pericarditis	♂	16	S., 92	?	?	Radial	Occurred after 6 days of digitalis; did not recur after withdrawal	0.10, 1.16, 1.70, 0.76, 0.60, 0.56	0.56 to 0.74
	3. Mitral stenosis; cardiac decompensation	♀	24	S., 95	0.4 to 0.7	+	Jugular; radial	First noticed 2 days after digitalis	0.70, 0.72, 1.56, 0.76, 0.74, 0.70, 1.56, 0.76, 0.66	0.66 to 0.76
	4. Aortic insufficiency; cardiac decompensation	♂	65		0.30		Jugular; radial	After 4 days of digitalis	1.48, 0.98, 1.48, 0.96	Cannot be determined
Wenckebach	1. No disease	♂	30		0.3 to 0.4	+	Jugular; radial	Not stated, but probably not given	0.78, 0.60, 0.68, 0.70, 1.18, 0.78, 0.66	0.66 to 0.78
	2. Cardiac decompensation without valve lesions		?	+	0.3		Jugular; radial	Not stated, but might have been given	0.92, 1.86, 0.88, 0.82 ...	0.76 to 1.00
Hewlett....	Chronic alcoholism; hepatic cirrhosis; arteriosclerosis	♂	41		0.25 to 0.4		Jugular; radial	Had digitalis for 10 days before arrhythmia was observed	1.04, 1.04, 1.85, 1.84, 1.09, 1.04	1.03 to 1.08
Gibson	Cardiac decompensation	♀	66	S., 150 D., 80	0.7	+	Jugular; radial	Not stated	No blocked sinus beats	Cannot be determined
Ribl	Chronic endocarditis, decompensated	♀	63	S., 120	0.24	—	Jugular; radial	Had digitalis for 7 days before observed	0.66, 1.30, 0.70, 0.66, 1.12, 0.70	0.66 to 0.76
Lamlett	Chronic myocarditis	♀	40		0.2	?	Jugular; radial	Not related to digitalis	1.20, 1.16, 1.20, 1.08, 1.12, 1.80, 1.08, 1.20, 1.10, 1.30	1.08 to 1.30
Richold	1. Severe typhoid	♂	23				None	Digitalis was given before arrhythmia appeared		
	2. Arteriosclerosis, decompensation	♂	67			?	None	After 3 injections of strophanthus		
Schott	Acute rheumatic fever; paroxysmal tachycardia	♂		S., 140 D., 85	0.2	+	Electrocardiogram; jugular radial	No digitalis used	0.76, 0.74, 1.04, 0.74	No sinus variation
Levine	1. Chronic nephritis; hypertension	♀	40	S., 196 D., 98	0.14		Electrocardiogram; jugular radial	None used	0.86, 1.12, 0.80, 0.88, 1.08, 0.64, 0.88, 1.12, 1.08, 0.88	0.86 to 1.08
	2. Chronic endocarditis; marked decompensation	♂	17	S., 120 D., 90	0.16	+	Electrocardiogram; jugular radial	Arrhythmia first seen after 3 gm. of digitalis	1.80, 0.14, 0.72, 0.40, 2.00, 1.76, 2.10	1.60 to 2.72
	3. Chronic nephritis; chronic myocarditis; hyperthyroidism	♀	40	S., 171 D., 80	0.16 to 0.24		Electrocardiogram	Had taken a great deal of digitalis	0.62, 0.56, 1.14, 0.71, 0.56, 0.54, 0.58, 0.53, 0.55	0.54 to 0.56
	4. Chronic endocarditis; decompensation	♀	25	S., 90 D., 64	0.22 to 0.40	Probable	Electrocardiogram	Had taken a great deal of digitalis	0.80, 1.52, 0.82, 0.81, 0.80 ...	Absent.

* In this column ♂ denotes male and ♀ female.

attacks of rheumatic fever. About ten years ago he first noticed his heart thump violently after one of his "sprees." This lasted three days. He found that whisky would occasionally bring on these attacks. For the past eight months since an attack of pneumonia, he has been unable to work because of shortness of breath.

On physical examination the patient was found to be a stout rugged man. He sat up in bed, breathing rapidly and with some distress. The tonsils were red and ragged, the pharynx was congested. The heart was markedly enlarged; left border 20 cm. to the left of the midsternal line in the sixth interspace. The right border was 4 cm. to the right of the midsternal line in the fourth interspace. The action was regular. A systolic murmur could be heard all over the precordium, loudest at the apex. A diastolic murmur was heard along the left border of the sternum, but not at the apex or at the aortic area. Systolic blood pressure was 120, diastolic 90. The lungs showed numerous moist râles in both backs. In the abdomen the liver edge was felt 7 cm. below the costal margin in the right midclavicular line. A distinct fluid wave was present. There was marked edema of the scrotum and legs. Patellar, Achilles and plantar reflexes were normal. The Wassermann reaction of the blood was negative. The patient was given a Karrell diet. He took 0.015 gm. morphin and was started on 10 c.c. of an infusion of digitalis three times a day. January 5, two days after entrance, the patient had an attack of transitory auricular fibrillation during which time he felt very much worse. This attack was similar to those he described in his past history. January 29, he was given theocin, and a marked diuresis followed. The digitalis was discontinued for two days from January 29 to January 31, when it was again given in the same doses. February 1 he had two attacks of transitory auricular fibrillation which lasted only a few minutes. Two days later pauses were first noticed which were equal to two heart beats. The electrocardiogram showed this to be sino-auricular block. Digitalis was omitted, February 4, and on this day another paroxysm of fibrillation occurred, but this attack caused no discomfort, for the ventricular rate was slowed as a result of the digitalis action on the heart. From February 9 to March 13, digitalis was given in varying doses almost all the time. Several additional paroxysms were observed, but what were more interesting were the long pauses in the heart action, frequently preceded or followed by an ectopic ventricular beat. During these pauses, which were numerous, all chambers of the heart were inhibited. The length of the pauses was so nearly equal to a simple multiple of the normal heart cycle that it seems probable that there was a blocking of the impulses just below the pace maker. Generally the pause was equal to two beats, but occasionally longer ones were noticed. On one occasion there was total arrest of the whole heart for 3.45 seconds, which equaled five heart cycles. The patient was never bothered by these pauses, although he said that he knew the heart was skipping beats. He did well; his edema disappeared to a great extent, and he was able to walk about. He decided to leave the hospital against our advice. In three weeks he returned to the wards (April 13) in a desperate condition. He had general anasarca and was comatose. After rest in bed, digitalis and the taking of theocin, he recovered so that, May 22, 1915, he left the hospital much improved. During his second stay, he showed evidence of sino-auricular block on only one occasion, and had several paroxysms of auricular fibrillation similar to the ones observed previously. When seen in the outdoor department, Sept. 10, 1915, the patient was clinically the same as when he left the hospital, although he has been unable to work.

Case 3 (Medical No. 2218).—A. A., woman, aged 40, complained of cough, palpitation and weakness. Her family history was unimportant. She had had "goiter trouble" for many years, and frequently coughed. Recently the cough and palpitation had been getting worse. When she entered the hospital, January 24, the heart was absolutely irregular, somewhat enlarged and the blood pressure was 174 systolic and 80 diastolic. There were many coarse moist râles

at both lower portions of the lungs in the back. She showed evidence of hyperthyroidism in that she had exophthalmos, slight tremor of the hands, and a tumor in the region of the thyroid. She was given a great deal of digitalis (4.7 gm.) during the next two weeks. Two days after entrance the auricles stopped fibrillating and the heart action became regular. Several other attacks of transient auricular fibrillation were observed. February 11, pauses of the heart action equal to two cycles were observed which were due to S-A block. At this time the digitalis had also affected the A-V node, causing a P-R interval of 0.24 second. This patient has not been heard from since she left the hospital.

(Medical Nos. 2279 and 2696).—K. F. W., woman, aged 25, complained of shortness of breath. The family history was unimportant. She had had vague rheumatic pains in the right leg. For the past year there had been gradually increasing weakness, palpitation and shortness of breath. Physical examination was unimportant except for the heart, which was enlarged and gave evidence of a constricted and incompetent mitral valve and a relatively incompetant tricuspid valve. The blood pressure was 90 systolic and 64 diastolic. The patient stayed in the hospital from February 4 to April 12, 1915. She took digitalis during this time. The heart rate slowed, and an increase in the P-R inter-

Fig. 1.—In all these tracings the lead is indicated in the upper left hand corner, the time is in one-fifth and in one-twenty-fifth second, and the deflections are such that 1 millivolt = 1 cm. Case 1, Leads I, II and III, taken Dec. 12, 1915; sino-auricular heart block. The figures above the curves are the R-R intervals; those below are P-R intervals.

val occurred. She was again admitted, April 26, 1915, in the same condition as she was in the first time. She was given digitalis again. The length of A-V conduction increased to the extent of a 2 to 1 heart block. May 10, an electrocardiogram was taken which showed not only delayed A-V conduction but also occasional blocked sinus beats. Digitalis had probably affected both S-A and the A-V nodes in this case. Decompensation gradually became more marked, and the patient died, June 20, 1915.

EXPLANATION OF THE ELECTROCARDIOGRAMS AND DISCUSSION

Figure 1 gives the electrocardiogram of Case 1 taken by the usual three leads, Dec. 12, 1914. With every auricular contraction (P) there is a ventricular contraction (R and T), while during the long pauses no waves appear. The normal heart cycle at this time varies from 0.88 to 1.08 second. This variation could be due to a change in

the rate of the pace maker or to changes in the time it takes the impulse to go from its origin to the auricular musculature. It cannot be entirely due to the latter, for then one would expect the P-P interval to become gradually longer until one sinus beat is blocked. Here the P-P intervals become shorter almost invariably just before a pause, as if the conduction of impulses improve. Occasionally (Fig. 1, Lead I third to eighth cycles) the intervals lengthen from 0.88 to 1.07 second, and later shorten without resulting in a blocked beat. One impulse finally is blocked after a short beat. It seems therefore that, although there probably are changes in the S-A conduction, if one is permitted to draw any analogy from the a-v conductive system, these alone are not sufficient to account for the heart block. The other factor is a sinus arrhythmia. When the heart accelerates during sinus arrhythmia, the conduction from sinus to auricle experiences fatigue. Finally, conduction becomes so difficult that sinus impulses are blocked. In this event, we expect the cycle before the blocked beat to be short, and the first one to appear after the block to be long; but on account

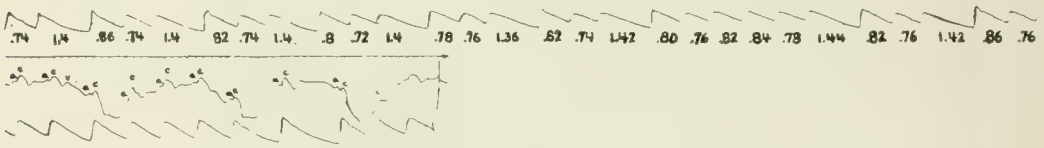

Fig. 2 (Case 1).—Radial and jugular tracings taken Dec. 12, 1915. The blocked beat is generally preceded by a short cycle and followed by a long cycle.

of the rapid and irregular rate of impulse formation just at the time the beat is blocked, the pause does not equal exactly two normal cycles. These points are illustrated by almost all the tracings taken of the patient over a period of five months, and by many of the other cases in Table 1.

In the polygraphic tracings of Figure 2 there is fairly regular blocking of every third impulse after a cycle of about 0.75 second. The length of the pause averaged 1.40 second, and the cycle after the pause, 0.82 second. If the impulses at this time followed each other in 0.72 second, they would be conducted; but if the interval was shorter, for example, 0.70 second, the second impulse would be blocked. The only time that the third beat in Figure 2 was not blocked occurred after a comparatively long cycle, 0.76 second. The ease with which impulses could be conducted was not always quite constant. On other days, impulses were blocked more readily. The shortest cycle that was not blocked in Figure 1 was 0.86 second, which shows that impulses were not conducted as well that day. A point of additional interest is that

when two pauses come in succession, the second is almost always longer than the first (see Fig. 1). This follows from the foregoing consideration, that is, as the sinus rate accelerates, a beat is blocked, then one comes through, and the next beat is again blocked; during this time the sinus rate has been gradually decreasing in spite of the fact that the sinus rate is still rapid, and this causes the second pause to be longer than the first.

One must consider possible changes in S-A interval as well as changes in the sinus rate. If the sinus region is so impaired that some impulses are blocked, it is reasonable to assume that the impulses which are not blocked are transmitted with greater difficulty than normally just as is the case in defective A-V conduction. The normal S-A interval is about one-fourth of the P-R interval, that is, from 0.03 to 0.04 second according to Eyster and Meek.[6] May it not be that because this interval is so short, it can be greatly prolonged without causing any block? An attempt was therefore made to detect the sinus wave if present and thereby determine the S-A interval. Trac-

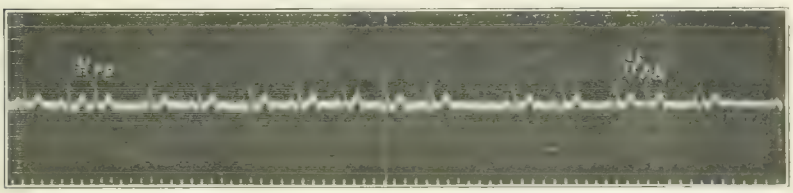

Fig. 3 (Case 1).—Lead II, December 15, before exertion. Sino-auricular block and occasional premature auricular beats (P. B.) are present. Ventricular rate is 61.16.

ings were taken with the fiber standardized so that 1 millivolt was equal to 3 cm. deflection and the photographic paper was moving rapidly. The peripheral resistance was only 500 ohms, which made it possible to have the string very sensitive and yet not too loose. No evidence of any sinus wave could be detected by this means.

The rate of occurrence of impulses is one factor which contributes to the incidence of block; and so it follows that if you accelerate this rate, the S-A interval might be lengthened and many impulses would be blocked. The patient was therefore asked to lift herself in bed from a reclining to an upright position twelve times. Tracings were obtained immediately before and after the exercise (Figs. 3 and 4). As was expected, a condition of bradycardia resulted. The auriculo-ventricular rate before exertion was 61.16; after exertion the rate for the first twelve beats was 48.52. There were nine consecutive cycles (interrupted only in one place by a short beat) which averaged 1.39 second in length, that is, a rate of 43.17. This result is explained by

supposing that the sinus rate increased and that every second impulse was blocked. As the patient recovered from the exercise and her sinus rate slowed, the number of blocked beats became fewer and she gradually returned to her original condition. The patient herself had observed this phenomenon. She complained that if she moved about, she was more troubled with "jumping heart" than when she remained quiet. The cause of the "jump" was the forcible beat following a long pause. There were more such beats when she exerted herself.

The activity of the vagus nerves was studied to see whether there was any hypervagotonicity or hypovagotonicity present. Figure 5 presents two tracings taken April 23, 1915, showing the effect of right and left vagal pressure. The right inhibited the heart very markedly, while the left inhibited it only slightly. This difference was repeatedly

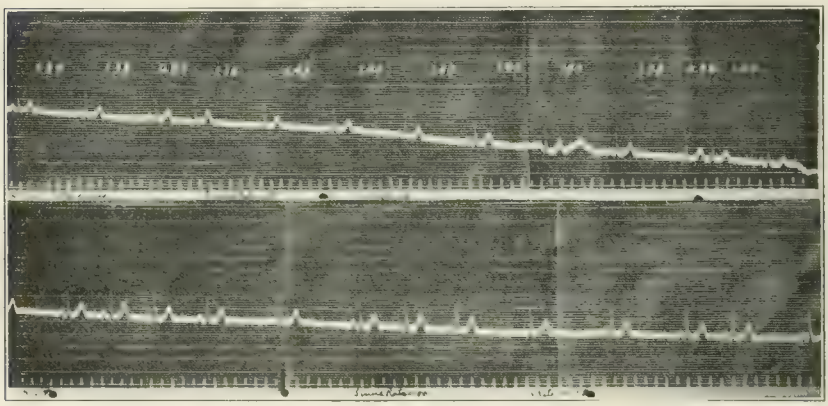

Fig. 4 (Case 1).—Lead II, after exertion. Ventricular rate is 43.17. Lower one taken a few minutes later shows return to original condition.

observed. In Figure 5 *a* the first beat after pressure was started is a ventricular beat not preceded by any auricular complex. The beat is supraventricular in origin because of its normal form. The R wave, however, is distinctly higher than the R waves which are preceded by "P" waves, and therefore it is quite probable that an auricular wave is here buried with the ventricular, increasing its amplitude. Similarly the next beat, which comes after a pause of 5.14 seconds, has a higher R wave than the others and is not preceded by a P wave. These are most likely nodal or at least escaped ventricular beats, arising in some supraventricular focus. The following beat, marked P. B., is difficult to interpret. It comes prematurely and one might say that the T wave just before is a little different in form from the others, which would be explained by considering that an auricular beat were superimposed on the T wave, that is, the auricles had been released from vagal inhibi-

tion. From then on the heart returned to its normal rhythm. Left vagal pressure (Fig. 5 *b*) had a much slighter inhibitory effect. The second beat after pressure was started is an escaped ventricular beat just as above, but here coming 0.08 second after the auricular beat. It is too short a P-R interval to be accounted for by the ordinary conduction of an impulse from auricles to ventricles, especially during left vagal pressure, when there is considerable evidence that the left vagus has a distinct primary negative dromotropic effect on the heart (Robinson and Draper,[27] Levine[28]). The following beat is a similar one except that the P wave comes on the down stroke of the R rather than before it. It follows, then, that the auricles and ventricles were contracting independently or that they were responding to the same stimulus arising in the junctional tissue between them. It is unlikely that

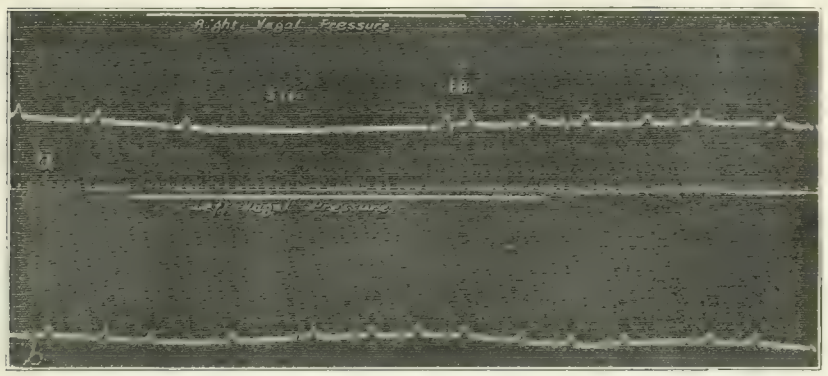

Fig. 5 (Case 1).—Effect of right and left vagal pressure. The signal above marks the duration of pressure. Escaped ventricular beats with simultaneous contraction of auricles are seen. The right caused more profound inhibition than the left.

they were dissociated, because such beats occurred quite frequently, and one ought to find auricular beats in ventricular diastole.

During the second stay in the hospital it was thought that if exercise caused a bradycardia, atropin might have the same effect. Two experiments were made on different days. The first time 0.001 gm. of atropin sulphate was given, subcutaneously, and the second time 0.0015 gm. was given. The results of the two experiments were practically identical. Figure 6 gives a graphic account of the experiment. The first

27. Robinson, C. G., and Draper, G.: Action of Vagus Nerve on Human Heart, Jour. Exper. Med., 1911, xiv, 217.

28. Levine, S. A.: The Oculo-Cardiac Reflex, an Electrocardiographic Study with Special Reference to the Difference between Right and Left Vagal and Ocular Pressures in Tabetics and Non-Tabetics, The Archives Int. Med., 1915, xv, 758.

tracing was taken one minute before the injection and shows S-A block. The second tracing of Figure 6 was taken twenty-five minutes after the injection and shows a rapid heart action at the rate of 78.59, and that the heart block has entirely disappeared. The rate increased to 87 a little while later, and at the height of the atropin effect the condition of the vagus nerve was studied to see if there was complete atropin release. Right vagal pressure caused distinct inhibition of the heart (Fig. 6, third curve) in spite of the rather large dose of atropin given.

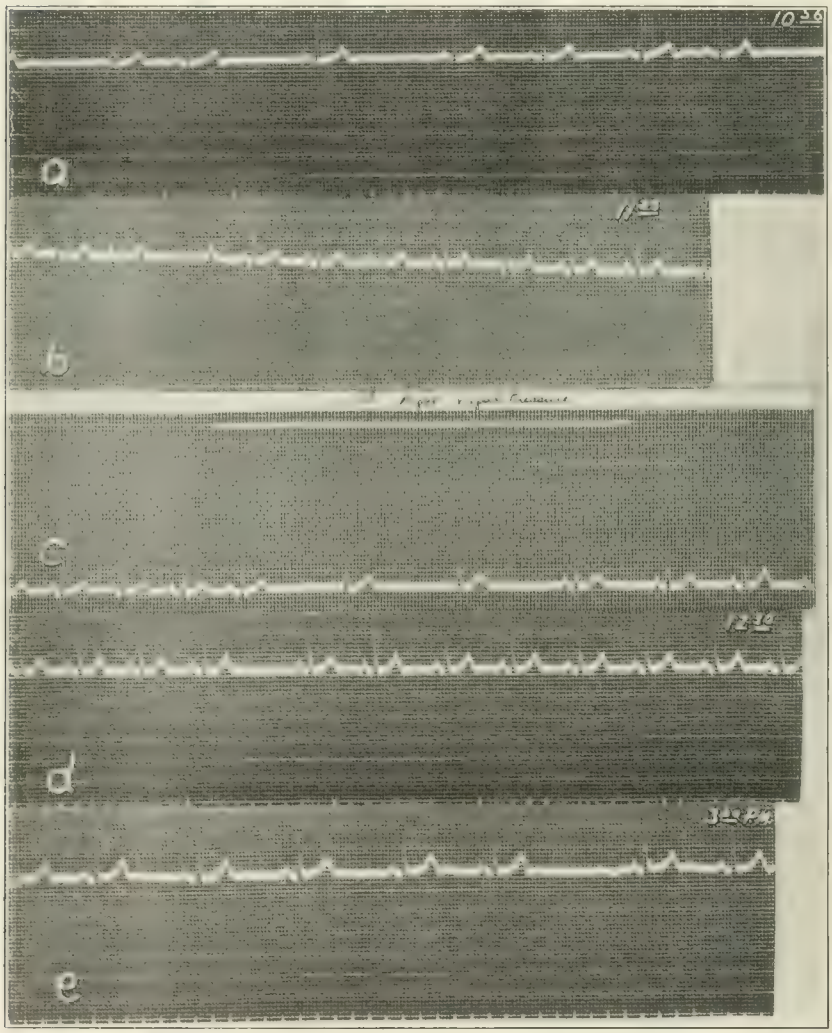

Fig. 6 (Case 1).—The course of the heart's action under atropin: c (taken at the height of the atropin effect) shows that the vagi were not completely paralyzed. Atropin makes the arrhythmia gradually disappear.

Evidently the vagi were not entirely paralyzed by the atropin. The last two tracings of Figure 6 show how the heart gradually returned to its former rhythm. Table 2 gives the apex rate (counted for a minute each time) taken during the experiment.

TABLE 2 APEX RATE

Time	Pulse Rate
10:52	54
Atropin, 0.0015 gm., at 10:57	
11:00	54
11:09	50
11:15	58
11:20	76
11:24	81
11:31	87
11:36	86
11:42	83
11:47	85
11:51	85
11:59	87
12:10	81
12:20	74
12:29	68
12:45	75
1:00	65
2:00	54

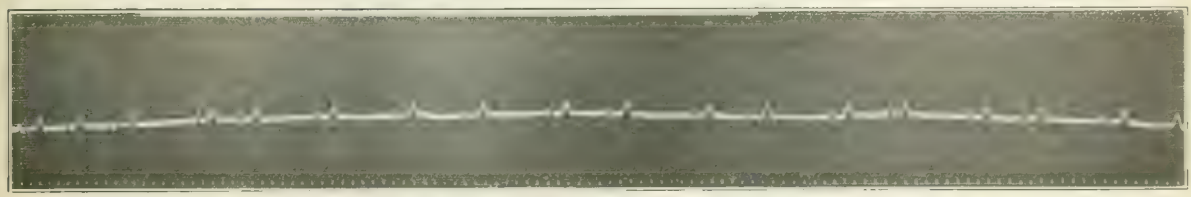

Fig. 7 (Case 1).—The signal marks the duration of deep inspiration. Numerous escaped beats probably arising in the junctional tissue appear.

It was expected that acceleration of the rate of the pace maker would result in the blocking of every other impulse as happened after exercise. The explanation suggested for the different result is that atropin increased the conductive power of the S-A node. Ritchie[29] thought that atropin has this effect on the A-V conductive system. On the other hand, the degree of acceleration may not have been sufficient to bring about increased blocking. If the sinus rate had reached 90 or more, block might have resulted.

Holding a deep breath altered the heart's rhythm (Fig. 7). The auricular rate decreased. Numerous abnormal beats occurred similar to those of Figure 5. It is evident that the ventricles readily escape

29. Ritchie, W. T.: The Action of the Vagus on the Human Heart, Quart. Jour. Med., 1912-1913, vi, 47.

by starting an inherent rhythm in the absence of impulses coming from the auricles. These beats resemble those recently published by Wilson,[30] which were also obtained under false respiration.

In Case 1, an elderly woman who had hypertension and slight impairment of the kidney functions manifested a persistent arrhythmia which appears to be sino-auricular block. No digitalis was taken at any time. Figure 8 gives a graphic description of the probable time rela-

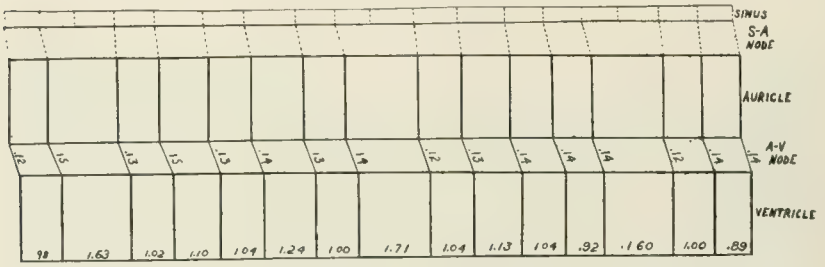

Fig. 8 (Case 1).—A diagrammatic representation of a tracing of Case 1, taken April 23. The dotted lines above are the probable sinus impulses with the corresponding S-A intervals. The auricular and ventricular time relations were taken from an electrocardiogram. There is a slight sinus arrhythmia and gradual lengthening of the S-A interval.

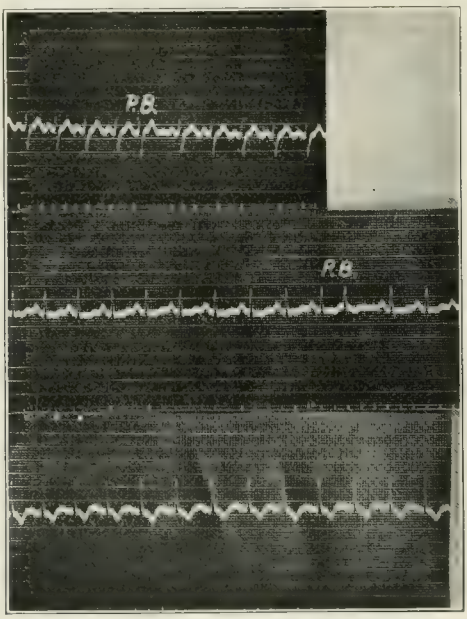

Fig. 9 (Case 2), Leads I, II and III.—Jan. 23, 1915. Premature auricular beats (P. B.) occur in Leads I and II.

30. Wilson, F. N.: Three Cases Showing Changes in the Location of the Cardiac Pace Maker Associated with Respiration, THE ARCHIVES, INT. MED., 1915, xvi, 86.

tions of the heart impulses. The auricular and ventricular beats and the P-R intervals were accurately measured. The timing of the sinus impulses and the S-A intervals are hypothetic. The heart was readily inhibited by right vagal pressure, and 0.0015 gm. of atropin made the arrhythmia disappear. Exertion, however, caused bradycardia.

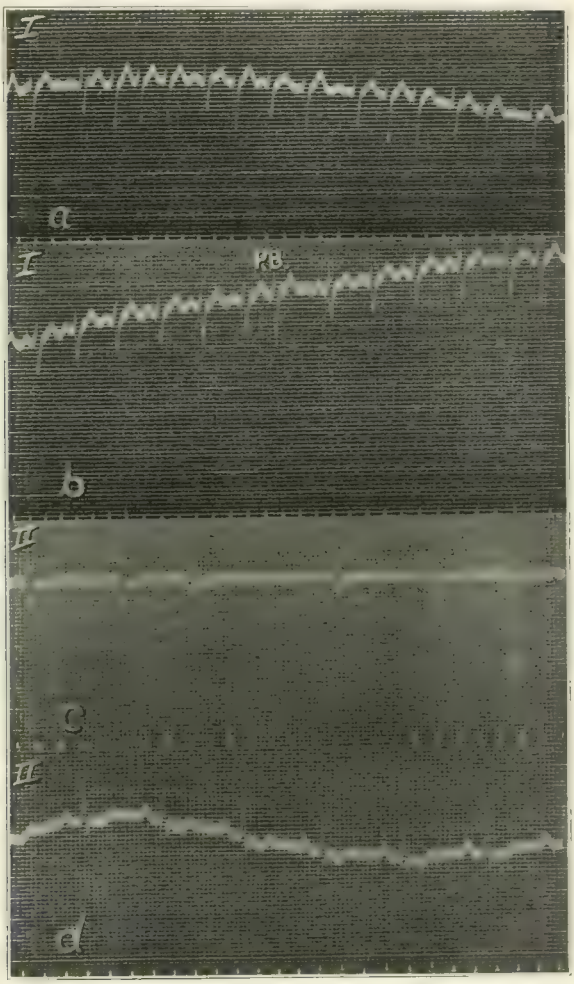

Fig. 10 (Case 2).—*a*, January 25, 3 p. m., shows an attack of auricular fibrillation; *b*, January 25, 4 p. m., shows a normal heart mechanism except for occasional premature auricular beats; *c*, February 4, 10 a. m., shows auricular fibrillation with slow ventricular rate; *d*, February 4, 4 p. m., shows a normal heart mechanism.

Case 2 showed an entirely different type of sino-auricular block. The heart beat rapidly at the rate of 115.4 (Fig. 9). Premature auricular beats (P.B.) are seen in Leads 1 and 2. The curves indicate pre-

dominant hypertrophy of the right ventricle. The patient had several attacks of transitory auricular fibrillation. Fifty minutes after the attack shown in Figure 10 *a* the auricles stopped fibrillating but developed occasional premature beats (Fig. 10 *b*). Between January 25 and February 4 the patient received 3 gm. of digitalis. The ventricular rate during the attack of fibrillation, February 4, was 79.8 (Fig. 10 *c*), while the rate during the first attack was 139.9. This demonstrates in a striking way the usual effect of digitalis on auricular fibrillation. February 3, a pause of 1.56 second was observed between two P waves which was approximately twice the length of the following beat (Fig. 11 *a*). The pause was due to blocking of the impulse at the sinus node. The sinus rhythm was not disturbed. After a premature auricular beat (P in Fig. 11 *b*), there was a pause of 1.73 second. This pause

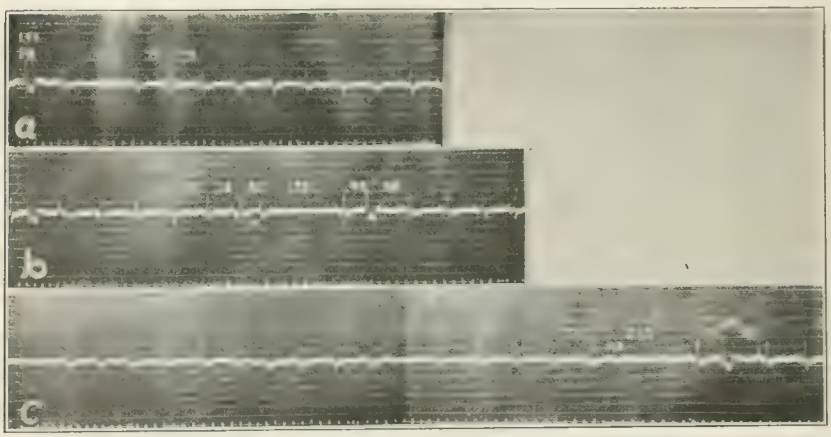

Fig. 11 (Case 2).—Numerous pauses due to sino-auricular block, which are generally preceded or followed by a premature beat.

consisted of two portions, one due to the preceding premature beat, and the second to the S-A block. The sum of these two intervals, 2.16 seconds, is exactly equal to three times the preceding normal interval, 0.72 second. Frequently after premature ventricular beats, a pause occurred which together with the pause just preceding it equaled 2.15 seconds. This interval is equal to three normal P-P intervals (Fig. 11 *c*). Abnormal ventricular beats were almost always followed by sinus blocks. They often recurred directly after the pause. The relation between these ectopic beats and the S-A block is not clear.

Periods of simultaneous sino-auricular block and idioventricular rhythm were also encountered. The auricles beat infrequently, and when that occurred, the ventricles developed their inherent rhythm. R_6, R_7 and R_8 (Fig. 12) are idioventricular beats. R_9, an ectopic ven-

tricular beat, then follows. The slow ventricular rhythm is resumed except for one interruption at R_{11} up to R_{15}; R_{15} is preceded by a P wave. From R_{15} on, the auricles and ventricles beat in normal sequence. Figure 12 *c* shows a very long period of inhibition which resulted from the blocking of four sinus impulses. It illustrates quite clearly that sudden death by "cardiac failure" in some cases might possibly be due to blocking of impulses at the S-A node, with failure of the auricles and ventricles to take up their rhythm.

In Case 2, a middle aged man who had chronic valvular disease showed during the administration of digitalis, which was given him in great quantities, irregular degrees of block at the S-A node. Pauses the length of two, three, four and five normal heart cycles were

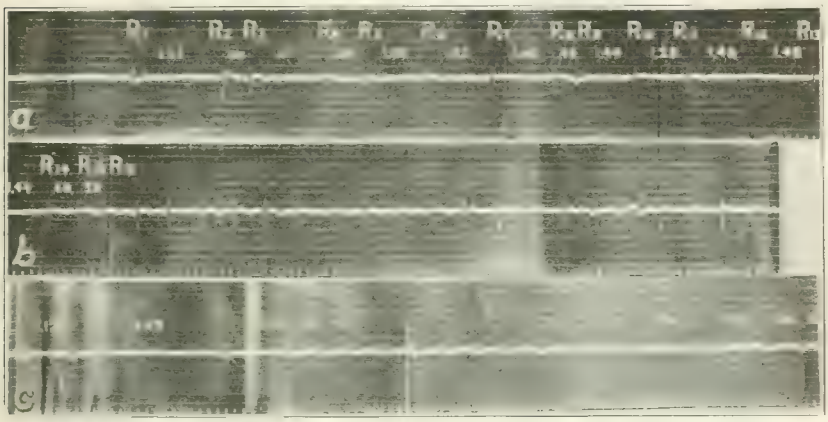

Fig. 12 (Case 2) — *a* and *b* are consecutive. After a long pause, the beginning of which was not photographed, there was complete blocking of sinus impulses for many seconds, except for two interruptions, during which time an idio-ventricular rhythm was started. A tracing taken some minutes later shows several pauses of different lengths; the longest, 3.45 seconds, resulted from blocking of four sinus impulses.

observed in the electrocardiograms. In one tracing the sinus impulses were blocked over a period of many seconds during which time the ventricles took up a slow regular rhythm of their own. Many of the pauses were related to premature ventricular beats which came immediately before or after the pauses.

Cases 3 and 4 (Figs. 13 and 14) are further examples of sino-auricular heart block occurring during the administration of digitalis. Case 3 had attacks of transitory auricular fibrillation as well. Both of these tracings show the effect of digitalis on the A-V system as well as on the S-A node, in the prolongation of the P-R intervals.

Impairment of conduction in the region of the sino-auricular node, then, is not an infrequent result of the action of digitalis. Just as digitalis is thought to have a more marked effect on A-V conduction when the A-V node is damaged, fibrous or other pathologic changes in the S-A node may predispose this site to disturbances such as have been noted in these cases. The relation of this disturbance to auricular fibrillation it is impossible to state. It is significant that two of the four cases here reported, and two of the fourteen cases reviewed here (Laslett[23] and Riebold[24]) had attacks of transitory auricular fibrillation.

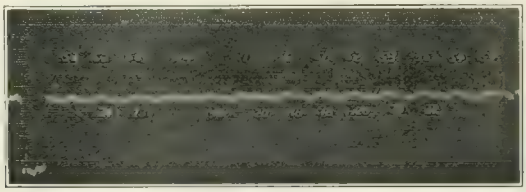

Fig. 13 (Case 3).—A blocked sinus beat is shown with a pause of 1.14 second, which is twice the normal heart cycle. The upper figures are the P-P intervals, the lower are the P-R intervals. The P-R intervals are somewhat prolonged. (The standardization is photographed at the beginning of the tracing.)

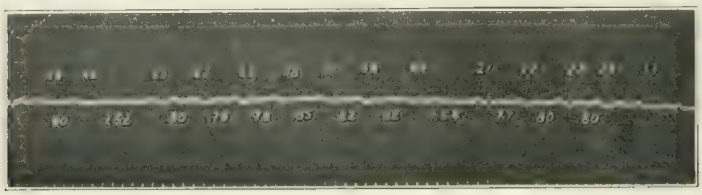

Fig. 14 (Case 4).—Two blocked sinus beats as well as prolonged P-R intervals. The upper figures are the P-R intervals; the lower are the P-P intervals. The pauses are slightly less than the length of two normal cycles.

SUMMARY

Delayed conduction at the sino-auricular node cannot be recognized until it is of a degree sufficient to cause blocking of impulses. It is probable that the condition of delayed S-A conduction without block is of much greater frequency than heretofore has been thought to be the case. Of the fourteen cases collected from the literature and of the four described here, the arrhythmia was observed after digitalis was given in ten cases, that is, 56 per cent.; and it disappeared when the digitalis effects had disappeared in these cases. In four of the other eight cases, it is stated or inferred that digitalis was not given, and in the remaining four no mention is made of the matter. Two of the latter were decompensated and might well have been taking digi-

talis before they were observed. Four cases manifested paroxysmal auricular fibrillation. This suggests that there is some pathologic change in the S-A node which enhances the effect of digitalis. Many of the cases showed a sinus arrhythmia more or less marked. In general, block at the S-A node occurs under the same conditions as block at the A-V node, that is, most commonly as a digitalis effect, also during acute febrile conditions particularly rheumatic fever, and finally in chronic myocarditis.

Four cases are described showing pauses of the heart's action which were equal in length to multiples of the normal heart cycle of the respective individual. There was no evidence of auricular activity during the pauses, which points to a blocking of the impulses above the auricles, that is, at the S-A node. The first case exhibited bradycardia on exertion. The ventricular rate fell to 43 as a result of acceleration of the sinus rate. Tracings taken over a period of five months showed that block depended on a slight sinus arrhythmia. Whenever the sinus rate increased beyond a certain point, the node failed to conduct the impulse to the auricles.

The three other cases showed S-A block only after digitalis had been taken; after it was withdrawn, the block was no longer observed. The second case described showed frequent pauses in which one, two, three or four heart beats were blocked. At one time there was observed in the electrocardiogram a condition of total sino-auricular block for many seconds while the ventricles were beating at their slow idioventricular rhythm.

Peter Bent Brigham Hospital.

SERUM SICKNESS IN A SERIES OF FIVE HUNDRED PATIENTS TREATED WITH DIPHTHERIA ANTITOXIN*

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With a view to ascertaining the frequency and severity of the various symptoms of serum reaction, five hundred patients receiving antitoxin serum were selected from the Louisa Minturn Hospital records. Consecutive cases were used, omitting only patients whose stay in the hospital was less than fourteen days, or whose complications masked the symptoms with which this paper is concerned. The antitoxin used was that dispensed by the New York Department of Health, so that the serum is somewhat modified.[1] Rash was taken as the determining factor in establishing reaction. It seems likely that there are cases which have no rash but give other symptoms, such as malaise, nausea, headache, pains in muscles, slight rise of temperature, etc. It is difficult to group these definitely. They come at the beginning of the second week of diphtheria when the patient begins to sit up out of bed and is put on a more extensive diet, and are associated often with constipation. These factors make the etiology of the mild disturbance difficult to determine. In the following series all patients with pronounced symptoms had a rash, so this forms a convenient and definite starting place.

Of the 500 cases, 422 patients received serum once, while seventy-eight were injected two or more times.

Frequency of Reaction in Cases Injected Once.—Of the 422 cases receiving one injection, eighty-four or 20 per cent. showed symptoms. Previous figures[2] have been from 8.1 to 54.6 per cent. The variations depend on the dosage, the serum itself, and doubtless on the care with which the patients can be watched. The frequency of the reaction increases with the increase in amount of serum given, as is shown by Table 1.

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* From the Department of Medicine, New York University and Bellevue Hospital Medical College and The Louisa Minturn Hospital.

1. Park, W. H., and Throne, B.: Trans. Assn. Am. Phys., 1906, xxi, 259.

2. Currie, J. R.: The Serum Disease in Man After Single and Repeated Doses, Glasgow Med. Jour., 1908, lxix, 277.

TABLE 1.—Showing Relation Between Dose of Serum and Number of Reactions

Number Cases in Group	Number c c Injected	Number Cases Showing Reaction	Per Cent. Cases Showing Reaction
20	1-3	3	15
294	4-10	50	17
106	11-15	29	27.37

In addition to the above case one patient received 20 c.c. and one 50 c.c. Both reacted.

Day of Disease of Serum Reaction.—The time of appearance of the serum reaction is shown in Table 2.

TABLE 2.—Time of Appearance of the Serum Reaction

Day of Disease	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
No. cases whole series	1	1	1	2	8	14	10	25	10	4	1	0	1	2	1	0	1
Receiving under 3 c.c.	..	..	..	..	1	1	1	.	..	.	..		..	..	..	..	..
Receiving 4-10 c.c.	..	1	.	2	6	7	4	15	6	3	1	.	3	..	1		1
Receiving 11-15 c.c.	1	..	.	.	1	6	5	10	3	1	.	..	..	2	..	..	
Receiving 20 and 50 c.c.	.	.	1	.	.	..	..	.	1	..	..	..	..	..	..	..	.

It would appear that there is no relation between the dosage and the time of appearance within the limits cited.

A second reaction was shown by four patients, one on the fifteenth day, two on the fourteenth day and one on the sixth day. The latter reacted first on the first day although there was no history of previous injection of serum. These cases all occurred in the 1 to 10 c.c group.

TABLE 3.—Character of Rash in Relation to Serum Dosage

Dose of Serum, c.c.	Number Cases	Number Urticarial	Per Cent. Urticarial	Number Erythematous	Per Cent. Erythematous
1 to 10	53	34	64.15	19	35.85
Over 10	31	29	93.54	2	6.46

Rashes.—Sixty-three, or 85 per cent. of the eighty-four patients had rashes of the urticarial type. The remaining twenty-one were erythematous. Of the sixty-three urticarial rashes, forty-three were severe and general in their distribution; twenty were mild and limited;

two of the severe cases showed small vesicles on the urticarial papules. Grouping these according to dosage, there is seen to be a marked increase in the urticarias with the increase in dose.

Nausea and Vomiting.—Sixteen patients, or 19.04 per cent., had nausea and vomiting. With increase in the amount of serum given there is an increase in the frequency and intensity of these symptoms.

TABLE 4.—Showing Increase in the Frequency of Nausea and Vomiting with Increase in Dosage

Dose of Serum, c.c.	Number of Cases	Number Having Nausea and Vomiting	Per Cent. Having Nausea and Vomiting
1 to 3	3	0	0
4 to 10	50	8	16
Over 10	31	8	25.8

TABLE 5.—Showing Duration of Vomiting in Relation to Amount of Serum

Amount of Serum, c.c.	Vomited Once	Nausea 1 Day, Vomited Several Times	Nausea and Vomiting		
			2 Days	3 Days	4 Days
All cases	4	7	2	2	1
4 to 10	3	3	0	1	1
Over 10	1	4	2	1	0

There were no cases of diarrhea. There were three cases of cramp-like pains in the abdomen.

Edema and Albuminuria.—Four patients had transient edema during the reaction. This is 4.76 per cent. Two of these were in the 1 to 10 c.c. group and two in the 10 plus group. Three of these involved the eyelids and one the lips. Of the three which showed swelling about the eyes, the tongue also was involved in one and another had at the same time some slight edema about the ankles. Three of the four had a transient albuminuria during the edema. Three other patients of the series had albuminuria without edema, making six in all, or 7.14 per cent.

Temperature, Pulse and Respiration.—Twenty-five patients, 29.76 per cent., had some rise in temperature. One had a definite chill; 7 patients had rise of 99 to 100 F.; 11, 100 to 101; 6, 101 to 102; and 1, to 104. The pulse followed the temperature and the respiration showed little or no change.

Joints.—Thirteen cases had pain in the joints, 14.28 per cent.; 9 of these were of short duration with slight or no local objective symptoms; 4 were severe, with redness, swelling and considerable pain; 2 of these lasted three days; 1, four days; and 1, six days.

Reaction in Cases Receiving Serum More than Once.—Of the 78 cases receiving serum more than once, 60 patients were injected twice and 18 more than twice; 13 of the latter received three injections. There were 5 remaining cases which do not lend themselves readily to grouping. In all of these cases the reinjections were before the appearance of symptoms from the first injection.

The 60 patients injected twice received the serum after an interval of approximately twenty-four hours in every case. In 32 cases the dose was 3, 4, or 5 c.c. for each injection, so that the total amount of serum received by the patient was from 6 to 10 c.c.; 8, or 25 per cent., of these reacted. The appearance of the rash was as follows: Two cases the fifth day, 4 the eighth day, and 2 the ninth day. The rash was urticarial in 6 cases, of which 5 were general and severe. It lasted 1 day in 4 instances, 2 days 1 case, 3 days 1 case, 4 days 1 case and 6 days 1 case. There was slight transient albuminuria in one case; 2 patients showed rise in temperature, one to 100, the other to 102 F.

In 28 cases the maximal total dose of the two injections was 20 c.c., the minimum 11 c.c. In all except 3 the total was 15 c.c. or more; 10 of these patients, 35.71 per cent., reacted; 7 of the rashes were urticarial. They appeared later than after single or small repeated injections.

TABLE 6.—Time of Appearance of the Serum Reaction in Repeated Doses

Day of Reaction.....	6	7	8	9	11	13	14	20
Number of Cases.....	1	2	1	1	2	1	1	1

It seems from the above that an administration of horse serum in doses from 6 to 20 c.c. in two instalments twenty-four hours apart is not less likely to give serum reaction than the same amount given in one dose. This seems to hold true also in the small number of patients injected three times. Of 9 who were injected at twenty-four hour intervals with about 5 c.c. each time, 3 reacted; 2 with a severe general urticaria. Of 4 patients receiving larger amounts, total over 20 c.c. and under 40 c.c., 2 reacted.

Five cases remain which were difficult to classify and from which little can be deduced. They are tabulated below for the sake of completeness.

TABLE 7.—Analysis of Five Cases Not Included in Above Grouping

1st Injection, c.c.	2d Inj. c.c.	Interval Between Injections c.c.	3d Inj. c.c.	Interval	4th Inj. c.c.	Interval	5th Inj. c.c.	Interval	6th Inj. c.c.	Interval	7th Inj. c.c.	Interval	Results
20	20	1 day	..	..	..	..	..	..	..	..	..	..	General urticaria 3d day, lasted 1 day.
2	15	1 day	..	..	..	..	..	..	..	..	..	..	No reaction.
1	12	1 day	..	..	..	..	..	..	..	..	..	..	General urticaria 13th day, lasted 2 days.
3	10	8 hrs.	10	12 hrs.	10	1 day	10	1 day	10	2 days	5	2 days	Partial urticaria 9th day, lasted 1 day.
8	30	1 day	20	12 hrs.	20	12 hrs.	20	9 hrs.	..	..	..	..	No reaction.

SUMMARY

1. A varying proportion of patients receiving modified horse serum react with rash and other symptoms. The larger the amount of serum the larger the number reacting.

2. Most patients react from the fifth to the ninth day, though reaction may take place from the first to the seventeenth day and perhaps later. The time of reaction has no relation to dosage.

3. Rash may be erythematous or urticarial. The larger the dose the greater is the proportion of urticarial rashes. Vesicular urticaria is sometimes, though rarely, seen.

4. Nausea and vomiting occurs in about one in five reacting cases. It is more likely to occur and to be severe and prolonged if the dose of serum is increased.

5. Albuminuria and edema occur occasionally, either together or independently.

6. Joint symptoms occur in about 14 per cent. of reacting cases and may be severe.

7. If a given amount of serum be given in two or more doses, it seems not less likely to produce reaction than if given in one injection.

The above cases occurred in the services of the author and his associates in The Louisa Minturn Hospital. To Drs. W. H. Katzenach, Robert J. Carlisle, Thomas S. Southworth, Edmund L. Dow and Stafford McLean, the author expresses his indebtedness for permission to use such of the cases as came in their services.

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